Review Article

Allium vegetables: Traditional uses, phytoconstituents, and beneficial effects in inflammation and cancer

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Short running title: anti-inflammatory and anti-cancer properties of *Allium* vegetables

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ABSTRACT

The genus *Allium* comprises of at least 918 species; the majority grown for dietary and medicinal purposes. This review describes the traditional uses, phytoconstituents, anti-inflammatory and anticancer activity, and safety profile of six main species, namely *Allium sativum* L. (garlic), *Allium cepa* L. (onions), *Allium ampeloprasum* L. (leek), *Allium fistulosum* L. (scallion), *Allium schoenoprasum* L. (chives) and *Allium tuberosum* Rottler (garlic chives). These species contain at least 260 phytoconstituents; mainly volatile compounds–including 63 organosulfur molecules–, saponins, flavonoids, anthocyanins, phenolic compounds, amino acids, organic acids, fatty acids, steroids, vitamins and nucleosides. They have prominent *in vitro* anti-inflammatory activity, and *in vivo* replications of such results have been achieved for all except for *A. schoenoprasum*. They also exert cytotoxicity against different cancer cell lines. Several anticancer phytoconstituents have been characterised from all except for *A. fistulosum.* Organosulfur constituents, saponins and flavonoid glycosides have demonstrated anti-inflammatory and anticancer activity. Extensive work has been conducted mainly on the anti-inflammatory and anticancer activity of *A. sativum* and *A. cepa*. The presence of anti-inflammatory and anticancer constituents in these two species suggests that similar bioactive constituents could be found in other species. This provides future avenues for identifying new *Allium*-derived anti-inflammatory and anticancer agents.

***Key words*:** *Allium* vegetables; phytochemistry; ethnopharmacology; anti-inflammatory activity; anticancer activity

1. Introduction

Although previously classified under the Alliaceae and the Liliaceae families, the genus *Allium* currently belongs to the Amaryllidaceae family of monocotyledonous plants. This broad taxon comprises around 918 heterogeneous species endemics to the dry and temperate regions of the northern hemisphere. The plants are hardy perennials, featuring either true bulbs or less developed vestigial bulbs attached to rhizomes along with the presence of underground storage organs. Although the biogeographical zone of Iran-Turania can be considered as the primary evolutionary center for the genus, this quickly extended to the Mediterranean region and western North America, especially the Floristic Province of California. Today, *Allium* plants are widespread over the northern hemisphere (Sharifi-Rad et al. 2016). *Allium* species have a long history of use as medicinal plants. Most prominent among these species are *Allium sativum* L. (garlic,) *Allium cepa* L. (onions), *Allium ampeloprasum* L. (leek), *Allium tuberosum* Rottler (garlic chives), *Allium fistulosum* L. (scallion) and *Allium schoenoprasum* L. (chives). Ancient manuscripts like the Egyptian papyrus "Codex Elsers", dating back to around 1500 B.C., outlined at least twenty-two garlic-based preparations to treat a wide variety of ailments including headache, body weakness and throat conditions. In the fourth century B.C., the Greek physician Hippocrates recommended garlic to treat pneumonia and wounds, and also as a diuretic agent. During the first century A.D., the Indians compiled their century old medical knowledge into a single compendium entitled "Charaka Samhita" where both garlic and onion were recorded as diuretics and anti-rheumatic agents as well as remedies for cardiac, gastrointestinal and ophthalmic disorders. The Roman naturalist Pliny the Elder described sixty-one garlic-based preparations employed for various disorders, including loss of appetite, ulcers, rheumatism and hemorrhoids. He also described the potential medicinal effects of onion against twenty-eight pathological conditions. Such ancient records established the genus *Allium* as an important source of medicinal herbs and later contributed to its significant popularity among physicians and herbalists. Garlic was reported by St. Hildegard von Bingen as a natural cure for the treatment of jaundice in the eleventh century, whereas Paracelsus and Lonicerus described its antitoxic and vermifuge effects in the sixteenth century. The genus was recognized in the nineteenth century compendium of American herbal remedies and home cures. Today, garlic, onion and other closely related species from the genus *Allium* have become integrated in many herbal preparations and remedies to treat fever, headache, cold, cough, scurvy, asthma, influenza, tuberculosis, whooping cough, inflammation, meningitis, laryngitis, bronchitis, arthritis, infection, coagulation, arteriosclerosis, jaundice, small pox,

chicken pox, typhoid, measles, cholera, diabetes, hypertension, cancer, malaria, epilepsy and several other pathological condition (Fenwick et al. 1985). The beneficiary effects of the main species of *Allium* have been frequently associated with the organosulfur compounds they contain, especially methylic and allylic derivatives (Putnik et al. 2019). Many studies have demonstrated that these organosulfur constituents possessed significant pharmacological activity, especially anticancer properties (Scherer et al. 2009). Several other classes of secondary metabolites have been identified within the major *Allium* species, including flavonoids, anthocyanins, saponins, phenolic acids, amino acids, glutamyl peptides, small organic acids, fatty acids, steroids, vitamins and nucleosides. Interstingly, flavonoids and saponins have also been characterized with significant activity. Furthermore, *Allium* species have been widely used as edible food by humans for ages, and *Allium* is the world's seventh most farmed and consumed vegetable. Well-established epidemiological studies have reported that consumption of *Allium* species as part of the diet decreases the risk of various illnesses. The use of organosulfur compounds from *Allium* species for the development of new functional goods is also growing rapidly within the pharmaceutical, medicinal, and food manufacturing industries (Poojary et al. 2017; Fredotović Ž and Puizina 2019).

Inflammation is a normal biological response generated by the body to protect against infection, tissue injury and noxious stimuli. Although primarily beneficial in nature, any unnecessary or prolonged activation of this response may lead to a detrimental outcome. A chronic state of inflammation forms the pathogenic basis of many diseases, including rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, retinitis, multiple sclerosis, psoriasis and atherosclerosis (Goodnow 2007). Since ancient times, inflammatory conditions and related disorders have been treated with plants or plant-derived formulations. Apart from herbal products with direct anti-inflammatory activity, many natural products rich in anti-oxidants also display protective effects against inflammation (Mueller et al. 2010). The six species of *Allium* selected in this review have been used to treat inflammatory disorders, including respiratory infections and rheumatoid arthritis (Jafarian et al. 2007; Bora and Sharma 2009; Fowotade et al. 2017; Singh, Chauhan, et al. 2018; Añides et al. 2019; Jannat et al. 2019b). The inflammatory response is commonly associated with the over-expression of pro-inflammatory enzymes and mediators. Such chemical messengers and associated signaling pathways contribute to the development of certain cancer pathogenesis (Park HS et al. 2013). The anticancer activity of many naturally-occurring phytochemicals has been attributed to anti-inflammatory properties both in *in vitro* and *in vivo* studies (Kang J-H et al. 2005). Natural products have remained the principal source of novel anticancer drug

candidates capable of inhibiting proliferation, inducing apoptosis, suppressing angiogenesis, invasiveness and metastasis (Al-Snafi 2017). Garlic, onion, and leek have been documented throughout history for their effectiveness against cancer, especially due to the presence of organosulfur compounds and allylic derivatives (Seki et al. 2012; Park HS et al. 2013).

The current review aims to describe six main *Allium* vegetables *viz*. *Allium sativum* L. (garlic) *Allium cepa* L. (onion), *Allium ampeloprasum* L. (leek), *Allium tuberosum* Rottler ex Spreng. (garlic chive), *Allium fistulosum* L. (scallion) and *Allium schoenoprasum* L. (chive)., with respect to their taxonomy, distribution, ethnomedicinal uses, phytochemistry, anti-inflammatory and anticancer potential, and toxicology.

2. Methodology

Google Scholar and PubMed were explored extensively using relevant keywords such as "*Allium sativum*", "Garlic", "*Allium cepa*", "Onion", "*Allium ampeloprasum*", "Leek", "*Allium tuberosum*", "Garlic chive", "*Allium fistulosum*", "Scallion", "*Allium schoenoprasum*", "Chive", "Traditional use", "Ethnopharamcology", "Ethnobotany", "Phytoconstituents", "Chemical constituents", "Anticancer", "Anti-inflammatory", "Organosulfur" and "Toxicological study". Relevant peer-reviewed scientific articles were retrieved from repositories including Web of Science, Scopus, MEDLINE, ScienceDirect, SpringerLink, Wiley Online Library, Semantic Scholar and Europe PMC. All the articles were evaluated in terms of authenticity, reliability and relevance, and 96 articles were selected accordingly to be included in the current review. The "Accepted" plant names as well as all recognized synonyms for the respective species were stated as per the enumeration of The Plant List (version 1.1, 2013) (http://www.theplantlist.org/). All the phytoconstituents were verified through SciFinder and PubChem and their structures were illustrated accordingly using ChemDraw Ultra 15.0 as per standard ACS guidelines.

3. Taxonomy

Records in The Plant List currently show at least 2,014 scientific names of plant species under the genus *Allium*. However, only 918 of them are recognized as Accepted names for individual plants classified under this genus. The other 1,038 names are recognized synonyms, whereas 58 of them are still unresolved (The Plant List 2013). Plants of the genus *Allium* are perennial herbs characterized with tunicate bulbs. The bulbs are arranged either in solitary fashion or as clusters, which reform annually. Leaf blades generally appear as linear, terete, channeled, falt or carinate. Flowers are generally erect with six petal-like tepals

arranged in two whorls and six epipetalous stamens. Fruits mostly take the form of dehiscent loculicidal capsules containing black, finely cellular-reticulate seeds (Eckel 2010). Taxonomically, the classification of the genus *Allium* is very complicated, sometimes contentious and still ongoing. In recent years, DNA technology advances have provided new insights into the intra-generic classification of the genus *Allium* through recognition techniques. One of the most widely used markers for the differentiation of *Allium* species is the internal transcribed spacer (ITS) region, including the 5.8S rDNA and the two spacers ITS1 and ITS2 (Dubouzet and Shinoda 1998) (Mes et al. 1999; Gurushidze et al. 2008).

4. Distribution and traditional ethnomedicinal uses

Allium vegetables including chives, garlic, garlic-chives, scallion, onion and leeks are widely distributed worldwide, and have been used throughout history as part of the human diet and as natural remedies (Fredotović Ž and Puizina 2019). Their ethnomedicinal uses vary depending upon geographical locations and cultures. The various parts of different *Allium* vegetables and their specific ethnomedicinal uses have been summarized in **Table 1**.

4.1 *Allium sativum* L.

Allium sativum (Garlic) is popularly ingested for both culinary and medicinal purposes. It is used for microbial infections in Russian traditional medicine. Nigerian traditional practitioners use this species to alleviate abdominal discomfort, diarrhea, otitis media and respiratory tract infections. In India and Europe, garlic is used mostly to treat hay fever, cold and asthma (Fowotade et al., 2017). In folklore medicine, garlic is used to treat pulmonary earaches, flatulence, scurvy, leprosy and blood clotting ailments. Garlic bulbs have been reported traditionally as carminative, stimulant, antiseptic, anthelmintic, diuretic, diaphoretic, expectorant, aphrodisiac and anti-asthmatic. Garlic paste is applied topically for its rubefacient, febrifuge and vesicant properties (Mikali, 2010).

4.2 *Allium cepa* L.

Allium cepa (Onion) is used to treat cancer, bruises, vertigo, bronchitis, migraine, cholera, colic, influenza, earache, fever, high blood pressure, jaundice, pimples, dropsy and sores. It is also employed as anthelmintic, aphrodisiac, carminative, emmenagogue, expectorant, and tonic. Fresh onion juice is reputedly employed in various countries for pain and swelling associated with bee or wasp stings. The use of onions has also been reported as an adjuvant therapy in the management of diabetes (Bora and Sharma, 2009; Lee et al., 2014). Onion has

been recommended as a remedy for cancer, coronary heart disease, obesity, hypercholesterolemia, type 2 diabetes, hypertension, cataract, colic pain, flatulent colic, and dyspepsia (Corea et al., 2005).

4.3 *Allium ampeloprasum* L.

Allium ampeloprasum bulbs are used traditionally to treat various inflammatory ailments. A powder prepared from the bulbs is used in various countries for the treatment of cough, mucous secretion and sore throat. In traditional medicine, oral administration of the fresh juice of *A. ampeloprasum* is considered stomachic, digestive stimulant and antispasmodic (Dey and Khalid 2015). In Maranno tribal medicine, the whole plant is used against fever, teething discomfort in babies, infections, and inflammation (Añides et al., 2019). The plant is also employed to manage hypertension, and infectious and digestive disorders (García-Herrera et al., 2014).

4.4 *Allium fistulosum* L.

Allium fistulosum is used in traditional Chinese medicine as a potential remedy for the common cold, influenza, arthritis, headache, abdominal pain, constipation, dysentery, sores, ulcers, parasitic infestations, arthritis, and heart disease (Jafarian et al., 2007; Sung et al., 2018; Zolfaghari et al., 2020). In other areas of the world, the plant is used for similar ailments in combined applications with other closely-related species.

4.5 *Allium schoenoprasum* L.

Allium schoenoprasum is a common folk remedy for hypertension in Indonesia. In Asian folklore medicine, *A. schoenoprasum* is used to treat the common cold and pulmonary edema. It is also employed against sunburn and sore throat, as well as to increase appetite and digestion (Singh et al., 2018).

4.6 *Allium tuberosum* Rottl.

Allium tuberosum seeds are commonly used in traditional Chinese medicine to treat impotence and nocturnal emissions (Hu et al., 2006). They are also used as tonic and aphrodisiac. In contrast, the leaves of *A. tuberosum* are usually employed to cure abdominal pain, diarrhea, hematemesis, diabetes, snakebite and asthma. *A. tuberosum* root, bulb, leaves and cloves are used in Arunachal Pradesh (India) to treat the common cold and coughs, as well as a hair tonic and antilipidemic. In another region of India, the Meitei tribe uses a

decoction of the whole plant to relieve various gastrointestinal ailments. A poultice prepared from the whole plant is used commonly in India to heal spermatorrhea. The plant juice is used to stem severe bleeding. The Subanen tribe in the Philippines uses a poultice of the whole plant to alleviate fever. *A. tuberosum* is also used in the country to treat asthma. In Thailand and Indo-China, the seeds are used as a mouthwash to alleviate toothache through their antiseptic effect (Jannat et al., 2019).

5. Phytochemistry

The *Allium* genus is a rich source of volatile constituents comprising primarily of sulfur-containing compounds which have been associated with extensive biological properties (Guohua et al. 2009). In total, 63 sulfur compounds (**1-63**) have been characterized from the leaves and bulbs of the *Allium* species presented in this review (**Figure 1**). Another thirty volatile constituents (**64-93**) which do not feature a sulfur atom in their structures have also been reported from the leaves, seeds and bulbs of the species under consideration (**Figure 2**). Saponins are the second most abundant phytoconstituents in *Allium* species, with fifty-two saponins (**94-145**) covering a wide structural variation (**Figure 3**). Moreover, seven flavonoids (**146-152**), seventeen flavonoid glycosides (**153-169**), five anthocyanins (**170-174**) (**Figure 4**), and nineteen phenolic derivatives (**175-193**) (**Figure 5**) collectively represent the total phenolic contents of all six species together. Furthermore, six short chain organic acids (**194-199**), nine fatty acids (**200-208**) (**Figure 6**), four steroidal compounds (**209-212**) (**Figure 7**), eighteen amino acids (**213-230**), twelve glutamyl-peptides (**231-242**) (**Figure 8**), eleven vitamins (**243-253**) (**Figure 9**) and seven nucleosides (**254-260**) (**Figure 9**) have also been reported from the selected six species. All the phytoconstituents have been summarized in **Table 2** in categorical order.

6. Anti-inflammatory properties

Inflammation is an integral part of the body's defense mechanism and is initiated by a wide array of endogenous signaling molecules and exogenous pathogenic products through direct or indirect interactions with diverse classes of membrane receptors. Degradation products originating from the neutralization of invading microbes or damaged tissue are often recognized by a specific class of membrane proteins viz. toll-like receptors (TLRs). These receptors, in turn, facilitates the activation of several non-receptor-associated protein kinases (PKs) including interleukin-1 (IL-1) receptor associated kinase (IRAK), mitogen-activated protein kinase (MAPK), stress-activated protein kinase (SAPK) and Jun N-terminal kinase

(JNK). These, in turn, potentiate multiple transcriptional factors to enhance the translation of the inflammation-inducing proteins (pro-inflammatory molecules). A vast majority of such pro-inflammatory molecules is constituted by the regulatory hormone cytokines, commonly represented by transforming growth factor β (TGF-β), macrophage colony-stimulating factor (M-CSF), tumor necrosis factor α (TNF-α), IL-1 and IL-6. The pro-inflammatory cytokines can potentiate inflammatory and immune cells both in activity and number. Subsequently, a wide variety of transcriptional factors including nuclear factor-Kappa B (NF-κB), nuclear factor of activated T-lymphocyte (NFAT), signal transducers and activators of transcription (STAT) and Ca^{2+} response element binding protein (CREB), are further activated. In terms of effects, NF-κB can be considered as the main contributor of the inflammatory process as it can effectuate cytokine generation and enhancements, chemokine production and cell adhesion molecule expression. Chemoattractant cytokines (chemokines) promote the transfer or invasion of different leukocytes into the tissues whereas adhesion molecules facilitate their localization into the tissues through specific binding interactions. Based on the type of leukocyte they work on, chemokines can vary widely viz. monocyte chemotaxis/chemoattractant protein (MCP), neutrophil-activating protein (NAP)), eosinophil chemotaxis protein (ECP or eotaxin), macrophage inflammatory protein (MIP) and IL-8. The invasion of the immune cells into the tissues eventually leads to the propagation of inflammation into its more distinguishable phase. Apart from the immune cell-mediated pathway, inflammation can also be induced through the activation of certain enzymes which can, in turn, produce various cytokine-like local signaling molecules. Prominent among them are phospholipase A_2, cyclooxygenase-1 and -2 (COX-1 and COX-2), 5-lipoxygenase (LOX), inducible nitric oxide synthetase (iNOS), platelet-activating factor synthase and xanthine oxidase (XO). COX is responsible for the formation of pro-inflammatory hormones prostaglandins E_2 and $F_{2\alpha}$ (PGE_2 and $PGF_{2\alpha}$) whereas LOX generates leukotriene B_4 and C_4 (LTB_4 and LTC_4), all of which induce inflammation through interaction with G-protein coupled receptors on cell surfaces. On the contrary, the highly reactive radical species nitric oxide (NO) produced by iNOS acts through increasing the oxidative stress within cells leading to cellular alterations under inflammation (Kulinsky, 2007).

The anti-inflammatory potential of the six *Allium* vegetables under discussion has been often characterized in detail with their respective abilities to suppress one or more of the pro-inflammatory cytokines and enzymes. However, more effective inhibition of the inflammatory process could be achieved through direct or indirect reduction of the transcriptional effects of NF-κB, as such inhibition could eventually lead to the diminished

production of the pro-inflammatory cytokines *in situ* (You et al. 2019). Moreover, in certain cases, the anti-oxidative effects of either extracts or individual compounds could contribute to their anti-inflammatory potential through the minimization of the oxidative stress induced by highly reactive radical species (e.g. NO) (Parvu AE et al. 2014).

6.1 *Allium sativum* L.

Both the chloroform and methanol extracts of aged black garlic (ABG) exerted potent anti-inflammatory activity in human umbilical vein endothelial cells through the suppression of NF-κB activation and down regulation of COX-2 and PGE_2 levels (Jeong et al. 2016). In another study, the anti-inflammatory effect of ABG was attributed to the inhibition of toll-like receptor 4 (TLR4) signaling cascade and reduction of nuclear NF-κB level. Moreover, the ABG extract also led to a significant reduction in the activity of iNOS and COX-2, thus minimizing the production of NO, IL-6 and TNF-α in lipopolysaccharide (LPS)-stimulated RAW264.7 cell lines (You et al. 2019). In a previous study, a garlic powder extract (GPE) in dimethylsulfoxide at the concentration of 100 mg/L, was demonstrated to minimize the intracellular activity of pro-inflammatory cytokines IL-1β and TNF-α through the down regulation of NF-κB activity in human whole blood-based *ex vivo* system. Introduction of LPS into the blood swiftly promoted the release of IL-1β (15.7 ± 5.1 g/L) and TNF-α (8.8 ± 2.4 g/L) while administration of GPE significantly reversed the concentrations of IL-1 β and TNF-α to 6.2 ± 1.2 g/L and 3.9 ± 0.8 g/L, respectively. Based on this observation, it was suggested that GPE-modulated cytokine suppressions in blood supernatant cells may minimize the inflammatory response in adjacent tissues by reducing the pro- inflammatory activity of NF-κB (Keiss et al. 2003b).

For corroborating anti-inflammatory action, ABG extract was also studied 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced dermatitis mice model. It exerted substantial activity through minimizing the production of NO, IL-6 and TNF-α which accompanied with the reduced activity of iNOS and COX-2 enzymes (You et al. 2019).

The phytochemical investigation of GPE identified allicin and diallyl disulfide as the main anti-inflammatory molecules. Allicin, a major organosulfur constituent of *A. sativum*, was demonstrated to be capable of modulating immune cellular activity, especially that of T lymphocytes via the attenuation of SDF-1α chemokine and cell-mediated signaling pathways. Additionally, it also suppressed the pro-inflammatory trans-endothelial migration of neutrophils (Sela et al. 2004). Although it had no inhibitory effect on the production of IL-1β and TNF-α, but on the contrary it was capable to diminish IL-10 levels (Keiss et al. 2003b).

A recent study involving allicin also revealed its capacity to suppress the breakdown of IκB, an inhibitor of the transcriptional factor NF-κB. This in turn, attenuated the NF-κB-mediated boosting of inflammatory enzymes (COX/LOX) and subsequent synthesis of pro-inflammatory cytokines (Lang et al. 2004). Another noteworthy organosulfur metabolite of *A. sativum* named alliin was characterized with prominent anti-inflammatory activity in LPS-treated 3T3-L1 adipocytes. Alliin at the dose of 100 μM minimized the genetic expression of pro-inflammatory cytokines including IL-6, MCP-1, and early growth response-1 (Egr-1) as well as the translation of IL-6 and MCP-1. Moreover, the LPS-induced phosphorylation of extracellular signal-regulated kinase (ERK) was reduced in alliin-treated cells (Quintero-Fabián et al. 2013). Another sulfur-based phytochemical from garlic named diallyl sulfide (DAS), along with the non-sulfur phytoconstituent thymoquinone, also revealed potent capacities to halt inflammatory reactions by diminishing inflammatory cytokines (IL-1β, and TNF-α), and CYP-2E1 enzyme which further suppressed the formation of ROS (reactive oxygen species). Moreover, thymoquinone was found to be useful in the management of neurodegenerative disorders (e.g., Alzheimer's disease) as it impeded neuro-inflammation and amyloidogenesis by suppressing the NF-κB expression (Abdel-Daim et al. 2020). Another sulfur compound, diallyl disulfide at a concentration of 100 µM, markedly decreased the LPS-induced release of TNF-α and IL-1β (Keiss et al. 2003b). It was demonstrated to down regulate both the translation of pro-inflammatory cytokines and NO synthesis in a RAW264.7 murine macrophage cell line (Shin et al. 2013).The major active sulfur compound named, S-allyl cysteine regulated NO production through inhibiting iNOS expression in peritoneal macrophages and endothelial cells stimulated with LPS and cytokines (Kim K-M et al. 2001). Caffeic acid, S-allyl cysteine, uracil, diallyl sulfide, diallyl trisulfide, and other compounds from *A. sativum* were found to inhibit the intracellular expression of several pro-inflammatory cytokines including TNF-α, IL-1β, IL-6, MCP-1, and IL-12 through suppressing the transcription factor NF-κB (Arreola et al. 2015). Quercetin isolated from *A. sativum* was found to be capable of suppressing the intracellular concentration of NF-κB via modulating both the iNOS and COX-2 level at the concentration of 0.1 and 0.2 mM (Wadsworth and Koop 1999).

In vivo replication of the anti-inflammatory effect of allicin was achieved using the carrageenan-induced rat paw edema model in male Wistar albino rats. Allicin administered at the dose of 250 mg/kg body weight as a suspension in 2.0% Tween 80, suppressed acute inflammation in a comparable manner as the standard diclofenac sodium (Bose et al. 2013).

As several phytoconstituents of *A. sativum*, especially its organosulfur compounds, have already demonstrated potent and well-defined anti-inflammatory activity (**Figure 10**), future endeavors from the scientific community should focus on the clinical evaluation of these phytochemicals, individually and collectively. Further studies should also focus on determining the optimal extraction conditions to produce 'superior' extracts rich in bioactive volatile constituents, and on using chromatographic fingerprinting of different garlic extract to detect the molecules of interest. Such analytical investigation will facilitate the development of quality control protocols. The successful implementation of such studies could establish *A. sativum* as an effective herbal remedy for inflammatory conditions.

6.2 *Allium cepa* L.

The anti-inflammatory effect of the ethanol extract of *A. cepa* onion peel was investigated with a LPS-induced inflammatory model using the RAW 246.7 cell line. Cellular concentrations of iNOS, COX-2 and of the p65 subunit of NF-κB were determined by western blot analysis. The extract (when applied at concentrations of 0.1-100 µg/mL) suppressed the production of NO, iNOS, COX-2, NF-κB and mitogen-activated protein kinases (MAPKs) in a dose-dependent fashion. The highest experimental dose of this extract also diminished various pro-inflammatory cytokines including IL-6, TNF-α, and IL-1β by 44%, 53%, and 60%, respectively (Ahn et al. 2015). In a concurrent study, both the production of NO and the concentrations of pro-inflammatory cytokines including IL-6, TNF- α, IL-1ß were measured in a murine macrophage (RAW 264.7 cell line) to explore the anti-inflammatory response of onion peel hot water extract. The NO synthesis was reduced in a concentration-dependent manner using doses ranging from 0.1-100 µg/mL. At the highest dose, the extract suppressed the release of IL-6, IL-1β, and TNF-α by 38%, 34%, and 41%, respectively, compared to the control group (Kang B-K et al. 2015).

The anti-inflammatory effect of the extract was further confirmed *in vivo* as it significantly attenuated croton-oil induced ear edema in ICR mice at the dose of 100 mg/mL (Ahn et al. 2015). This was further translated into prominent *in vivo* anti-inflammatory activity in the croton oil-induced ear edema model in ICR mice with inhibition caused by the extract at the dose of 250 mg/kg body weight (Kang B-K et al. 2015).

The presence of inflamed airways obstruction has been previously linked to the pathophysiology of asthma. Abating the inflammation is a vital step in controlling the progression of this condition. A *Blomia tropicalis*-induced asthma model was used in A/J mice to evaluate the protective effect of *A. cepa* extract, and of its isolated compound

quercetin, against inflammation. The secretion of pro-inflammatory cytokines, including IL-4, IL-5, and IL-13 was elevated after stimulating splenocytes with pokeweed. Compared to the control group, the level of all cytokines except for that of IL-13, were remarkably suppressed by various doses of both *A. cepa* extract (10, 100, and 1000 µg/mL) and quercetin (3.75, 7.5, and 15 µg/mL) (Oliveira et al. 2015a).

Thiosulfinates and cepaenes from *A. cepa* were found to possess prominent anti-inflammatory activity. These compounds were demonstrated to suppress the chemotaxis of granulocytes to the inflammatory site, thus minimizing the onset of immune cell-mediated inflammation. Diphenylthiosulfinate exhibited the highest activity (Dorsch et al. 1990). In conclusion, both *A. cepa* and its constituents have been attributed with prominent anti-inflammatory properties for which underlying mechanisms have been characterized (**Figure 10**). Since a large number of volatile organosulfur and non-organosulfur compounds have been characterized from *A. cepa*, further investigation of such compounds for their anti-inflammatory potential is warranted. Additional studies should aim to optimize the extraction methods and analyze different *A. cepa* extracts to identify their optimum composition with respect to their anti-inflammatory potential.

6.3 *Allium ampeloprasum* L.

When investigated *in vitro* to evaluate the protective effect *A. ampeloprasum* extract in human mast cells (HMC-1), the extract at the concentration of 1.0 mg/mL, significantly suppressed pro-inflammatory cytokines TNF-α and IL-6 by 90% and 93%, respectively (Ko et al. 2013a). A steroidal saponin from *A. ampeloprasum* named ((3β,5α,6β,25R)-6-[(β-D-glucopyranosyl)oxy]-spirostan-3-yl-*O*-β-D-glucopyranosyl-(1→2)-*O*-[β-D-glucopyranosyl-(1→3)]-β-D-galactopyranoside) was investigated for its anti-inflammatory potential using a carrageen-induced paw edema model in Swiss albino mice. The extract suppressed the edema volume of mice paw prominently, indicating significant anti-inflammatory effect. This was further attributed to the capacity of the compound to modulate the secretion of histamine, serotonin and prostaglandins which are responsible for the generation of biphasic inflammation (Adão et al. 2011).

Contrary to the trend observed for other *Allium* vegetables where volatile compounds were identified as the major anti-inflammatory phytoconstituents, *A. ampeloprasum* yielded saponins with prominent anti-inflammatory activity. Since saponins are also prevalent among the other five species, this finding provides strong precedence for further research to be focused on evaluating the anti-inflammatory potential of different saponins found within

these species. The volatile constituents of *A. ampeloprasum* should also be subjected to both *in vitro* and *in vivo* anti-inflammatory screening. Comparative studies should also be attempted to ascertain whether this bioactivity is due to the volatile constituents, the saponins, or both combined.

6.4 *Allium fistulosum* L.

The aqueous extract of *A. fistulosum* significantly inhibited NO production by LPS-activated macrophages in a dose-dependent manner with a half maximal inhibitory concentration (IC_{50}) value of 213 µg/mL. The effect of this extract on the enzymatic activity of iNOS was also investigated. A dose of 2000 mg/mL, the *A. fistulosum* extract exerted 67.5% inhibition on the iNOS enzyme activity and also diminished the cellular expression of iNOS protein significantly (Tsai et al. 2005). Another study explored the anti-inflammatory activity of *A. fistulosum* in LPS-treated BV2 microglia cells. Four different extracts including the aqueous and ethanol extracts of the whole *A. fistulosum* and the aqueous and ethanol extracts of the root of *A. fistulosum* were investigated. In an MTT assay, all extracts except the ethanol extract of the root, effectively suppressed both the production of mRNA and the protein expression of iNOS and COX-2 enzymes at the concentrations of 50 µg/mL. The cellular concentrations of various pro-inflammatory cytokines, including TNF-α, IL-1ß and IL-6 were also significantly down regulated at the mRNA level (Park S-H et al. 2011a).

An *in vivo* investigation into the anti-inflammatory potential of the aqueous extract of *A. fistulosum* in the carrageenan-induced paw edema model demonstrated its prominent dose-dependent activity at concentrations of 0.25–1 g/kg body weight. The highest dose of the extract showed 29.6% reduction of the edema volume compared to the control group. The extract was also characterized with dose-dependant inhibition of lipid oxidation and NO production to the extents of 20–49% and 17–53%, respectively. The extract also showed a protective effect against inflammation through the enhancement of anti-oxidative enzymes including catalase (122–145%), superoxide dismutase (168–319%), and glutathione peroxidase (121–176%) in a comparable manner as the standard indomethacin (Wang B-S et al. 2013). Another study evaluated the effects of the methanol and chloroform extracts of *A. fistulosum* on the cell-mediated immune response in Balb/c mice. Both extracts at concentrations of 100 and 1000 mg/kg body weight exhibited significant reduction in the sheep red blood cell-induced paw swelling, which indicates potent anti-inflammatory activity (Jafarian A et al. 2007).

Although different *A. fistulosum* extracts demonstrated anti-inflammatory activity both *in vitro* and *in vivo* (**Figure 10**), the phytoconstituents responsible for this activity have yet to be identified and this warrants further investigations. The potential of this species in the management of chronic inflammation, as part as a healthy diet, should also be evaluated.

6.5 *Allium schoenoprasum* L.

When tested in the turpentine-induced rat inflammation model, aqueous solutions (25%, 50% and 100% w/v) of the leaf extract of *A. schoenoprasum*, the highest dose of the extract significantly reduced the phagocytic index (PI) and the phagocytic activity (PA). PI was recorded at 27 ± 3.18% and PA was measured at 52 ± 2.21 *E. coli*/100 leukocytes. The standard indomethacin significantly diminished PI (from 51.2 ± 2.12% to 17 ± 2.22%) and PA (from 177 ± 12.01 to 18 ± 2.84 *E. coli*/100 leukocytes). In order to ascertain the mechanism of such anti-inflammatory activity, different nitro-oxidative markers including total nitrites and nitrates (NOx), total oxidative status (TOS), total anti-oxidant reactivity (TAR) and oxidative stress index (OSI), were further evaluated. The extract, at concentrations of 50% and 100%, attenuated NO synthesis. This suppressed TOS and OSI values, and also reversed the down regulation of TAR, in a similar pattern as the standard indomethacin (Parvu AE et al. 2014). *In vivo* replication of such activity in appropriate animal model is necessary in order to ascertain the suitability of *A. schoenoprasum* as a traditional cure for inflammatory conditions. Moreover, the evaluation of the anti-inflammatory activity of *A. schoenoprasum* in terms of cyclooxygenase enzyme inhibition has yet to be established and warrants future exploration.

6.6 *Allium tuberosum* Rottl.

TNF-α-treated human umbilical vein endothelial cells (HUVECs) were used to ascertain the anti-inflammatory activity of *A. tuberosum* aqueous ethanol (70%) extract. This extract, at the dose of 100 µg/mL, diminished the mRNA expression levels of the intercellular adhesion molecule (ICAM)-1 and those of the vascular cell adhesion molecule (VCAM)-1 by approximately 48% and 58%, respectively. This extract, at concentrations of 50 and 100 µg/mL, also markedly reversed the TNF-α-stimulated protein expressions of both ICAM-1 and VCAM-1. Western blot analysis further revealed that the extract significantly reduced the TNF-α-induced phosphorylation of the NF-κB p65 subunit and the degradation of IκBα in vascular endothelial cells. It also reversed the increased adhesion capacity of monocyte to TNF-α-stimulated vascular endothelial cells by approximately 53% (Hur and Lee 2017).

The potential capacity of *A. tuberosum*-derived polysaccharides to minimize inflammatory reactions was evaluated in the adenine-induced chronic renal failure (CRF) model in mice. A polysaccharides-rich extract exhibited prominent dose-dependent activity, with the highest dose of 200 mg/kg per day down regulating pro-inflammatory cytokines *viz.* TNF-α, IL-1β and IL-6 by 36.4%, 35.1% and 36.1%, respectively. The extract also enhanced the mRNA expression levels of the anti-inflammatory cytokine IL-10 by 58.5% compared to those of the control group, demonstrating a clear beneficial effect on inflammation (Li Q-M et al. 2018).

Other than polysaccharides, no other individual anti-inflammatory phytoconstituent has been characterized from this species, warranting further bioactivity-guided phytochemical investigations into different *A. tuberosum* extracts in the future. Clinical studies of the long-term anti-inflammatory potential of this species, both in the diet and in herbal preparations, are also required. **Table 3** summarizes the potential of *Allium* vegetables in the management of inflammation and related disorders.

7. Anticancer properties

On account of the numerous ethnomedicinal records of *Allium* vegetables (including garlic, scallions, onions, chives and leeks) being used in cancer, a clinical investigation was performed to ascertain their protective effects against prostate cancer. The study revealed that consumption of these vegetables (at least 10 g per day) reduced the prevalence of prostate cancer compared to subjects who took less than 2.2 g per day. The occurrence of stomach and esophageal cancer was also demonstrated to be minimized following the intake of *Allium* vegetables (Štajner et al. 2011; Gao et al. 2018; You et al. 2019).

7.1 *Allium sativum* L.

The hydro-alcoholic (1:1) extract of *A. sativum* bulb enriched with polyphenolic compounds was investigated to estimate its inhibitory effect on breast (MCF-7), lung (A549) and ovarian (PA-1) cancer cell lines. The extract exhibited the strongest cytotoxicity against the MCF-7 cell line (IC_{50} value of 6.0 ± 1.0 µg/mL) while moderate to low activity was observed against A549 and PA-1 cancer cell lines (IC_{50} values of 15.0 ± 1.0 µg/mL and 28.0 ± 1.0 µg/mL, respectively) (Nema et al. 2014).

In another study, different garlic extracts *viz*. hot temperature garlic extract, low temperature garlic extract, black garlic hot temperature extract, fermentation garlic extract and UMPM (ultra-sonic waves, microwaves, micro bubble extraction) garlic extract, were

tested for their anticancer activity against RAW 264.7 and fibrosarcoma (HT-1080) cell lines. Both the low temperature garlic extract and the UMPM garlic extract demonstrated prominent dose-dependent activity against the HT-1080 cell line at concentrations of 125, 250, 500, and 1000 µg/mL. UG also suppressed nitric oxide production efficiently in the RAW 264.7 cell line, which was further associated with its anticancer effect (Kim H-J et al. 2010).

The sulfur-containing phytochemicals from *A. sativum* have potent anticancer activity against various carcinogens (Milner 1996). Diallyl disulfide (100 and 500 µM) was demonstrated to suppress the proliferation of human colon (HCT-15), lung (A549), and skin (SK MEL-2) cancer cell lines *in vitro* more prominently compared to SAC (S-allyl cysteine) (Sundaram and Milner 1996). Diallyl trisulfide exhibited stronger anticancer activity than diallyl sulfide and diallyl disulfide, stimulating caspase-3-mediated apoptosis through the enhancement of intracellular calcium ion concentration in the human colon adenocarcinoma (HCT-15 and DLD-1) cells lines (IC_{50} values of 11.5 and 13.3 µM, respectively) (Hosono et al. 2005). The garlic-derived sulfur-containing secondary metabolite Z-ajoene exhibited 38% and 42% reduction of tumor growth in mice and in sarcoma 180 and hepatocarcinoma cells, respectively (Li M et al. 2002). The antiproliferative effect of garlic oil was tested on the human promyelocytic leukemia (HL-60) cell line, and prominent activity was observed at a concentration of 20 µg/mL (Seki et al. 2000). In aflatoxin B1 (AFB1)-induced hepatic carcinogenesis in rats, treatment with diallyl sulfide (DAS) led to a strong decrease in mutagenicity by creating hydroxylated metabolites such as aflatoxin Q1 (AFQ1) and aflatoxin M1 (AFM1). However, treatment with diallyl disulfide (DADS) did not follow this pattern, but rather prevented AFB1-8,9-epoxide-stimulated mutagenicity and upregulated AFB1-glutathione conjugates levels in the cytoplasm. Diallyl disulfide along with diallyl sulfide (although to a lesser extent) led to the activation of glutathione S-transferase A5 (rGSTA5) and AFB1 aldehyde reductase 1 (rAFAR1), leading to enhanced detoxification of AFB1. Garlic-derived diallyl sulfide and diallyl disulfide effectuated their anticancer effects via changing both the phase-I and phase-II metabolic routes for AFB1 and stimulating respective enzymatic activities (Guyonnet et al. 2002). The protective effects of diallyl sulfide and diallyl disulfide against AFB1-induced DNA damage were further investigated. They prominently decreased cell death by upregulating the activities of GST and glutathione peroxidase (GPx) enzymes (Sheen et al. 2001). Therefore, organosulfur compounds might be the primary phytoconstituents of *A. sativum* which are responsible for its anticarcinogenic, antiproliferative, antimutagenic, cytotoxic and anticancer effects.

Further *in vivo* experiments are required to ascertain the anticancer activity and selectivity of the organosulfur constituents of *A. cepa*. Studies should also include further extensive work on a large number of closely-related organosulfur molecules in order to establish quantitative structure-activity relationships (QSAR). This would help design novel anticancer drug candidates in the future.

7.2 *Allium cepa* L.

Four extracts of *A. cepa*, including a petroleum ether, ethanol, ethyl acetate and aqueous extract, were investigated in mice 3T3-L1 pre-adipocytes and human breast cancer MDA-MB-231 cell line to evaluate their effect on fatty acid synthase (FAS) enzyme. The activity of this enzyme was enhanced remarkably in both cancer lines, especially the later one. The ethyl acetate extract displayed potent suppression of intracellular FAS activity at concentrations of 20-60 µg/mL for 24 hours. It also reduced intracellular FAS activity in MDA-MB-231 cancer cells by 32.1% and 56.3% at concentrations of 25 and 50 µg/mL, respectively, indicating dose-dependent activity. Similarly, the extract also diminished FAS activity in the 3T3-L1 cell line by 37.7%, 69.8% and 73.6% at concentrations of 20, 40 and 60 µg/mL, respectively, further establishing dose-dependent activity. Diminished intracellular FAS activity was associated with an enhanced apoptotic response, which was restored by palmitic acid. The viabilities of the MDA-MB-231 and 3T3-L1 cell lines were further assessed. Cellular proliferation was inhibited by the ethyl acetate extract in both cell lines with IC_{50} values of 52 and 81 µg/mL, respectively (Wang Y et al. 2012a).

Another *in vitro* study explored the anti-cancer effects of isolated polyphenols from lyophilized *A. cepa* in various human leukemia cells. The polyphenol fraction reduced cancer cell proliferation by inducing caspase-dependent apoptosis (**Figure 11**). The polyphenol fraction the TNF-related apoptosis-inducing ligand (TRAIL) receptor DR5 and suppressed the cellular inhibitor of apoptosis-1 (cIAP-1) in THP-1 and K562 leukemia cell lines (Han et al. 2013). In another study, the polyphenol content of *A. cepa* was demonstrated to inhibit cellular growth via up regulating p53 level, and subsequent Bax induction, as well as down regulating the anti-apoptotic (Bcl-2) protein (Lee WS et al. 2014). The polyphenol fraction efficiently reduced the cellular proliferation of U937 and AGS human cancer cells enhanced by the protein kinase B (PKB)/Akt. This suggested that the polyphenols of *A. cepa* had potent anticancer activity through inhibiting phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway and alterating the inhibitors of apoptosis proteins (IAPs) (Han et al. 2013).

Considering the presence of high amounts of flavonols and anthocyanins in *A. cepa*, their protective effect on DNA was evaluated in *E. coli* plasmid pUC19 using a single-cell gel electrophoresis (COMET) assay and on the breaking down of DNA by Fenton's reagent. DNA damage was significantly prevented by an extract of *A. cepa* at a concentration of 100 µg/mL. That same dose also showed potent antiproliferative activity in breast cancer and glioblastoma cell lines, with a more prominent effect observed in the later (Fredotović Ž et al. 2017).

A steroidal saponin, named Cepa2 and structurally similar to alliospiroside, was isolated from *A. cepa* roots. This compouind was investigated for cytotoxic potential against the P3U1 myeloma cancer cell line. It showed potent anticancer activity through attenuation of P3U1 cell proliferation by 91.13% in a time-dependent manner. Further exploration of Cepa2 as a potential anticancer drug lead are warranted (Abdelrahman et al. 2017b). Although it has been demonstrated that flavonoids in *A. cepa* have anticancer properties, the exact identification of the responsible phytoconstituents(s) is yet to be achieved. This species has also been demonstrated to possess a rich volatile content, especially organosulfur compounds. The latter have been reported from other species of the genus, especially *A. sativum*, and are known to possess anticancer properties. Therefore, both *in vitro* and *in vivo* experimentations into the flavonoid and volatile constituents of *A. cepa* are warranted in the future. The characterizations of the anticancer steroidal saponin Cepa2 has also provided some support to further investigate the steroidal and saponin constituents within this species.

7.3 *Allium ampeloprasum* L.

When tested on the osteosarcoma U2OS cell line, the extract of *A. ampeloprasum* demonstrated significant inhibition of cellular proliferation and metastatic proliferation. After treatment with the extract, approximately 66.7% of reduction in metastatic rate was evident (Dey and Khaled 2015). In another *in vitro* study, various concentrations (10-100 µg/mL) of the crude ethanol, methanol and water extracts of *A. ampeloprasum* were investigated for antiproliferative activity using a cell viability assay in human breast cancer (MCF-7) cell lines. The anticancer effect was observed over three days. The highest decline in cell viability was observed on the third day compared to the first and second days for all experimental doses. All extracts demonstrated minimum cell mortality at the dose of 50 µg/mL rather than 100 µg/mL. The methanol and aqueous extracts suppressed cell viability to 59.14 ± 2.64 and 47.16 ± 14.71%, respectively, at the dose of 50 µg/mL (Zamri and Abd Hamid 2019). As the anticancer effect of *A. ampeloprasum* extracts followed a non-linear trend with respect to

concentration, it was suggested that underlying dose-dependent toxicity may have contributed to this effect. In depth pharmacological studies are required in the future to explore the possible biochemical mechanisms involved in the anticancer activity of this species and clearly ascertain its safety profile.

Three new saponins (yayoisaponins A-C) and two known saponins (dioscin and aginoside) isolated from a new variety of *A. ampeloprasum* were explored for their cytotoxic potential. Among the isolated compound, only dioscin exerted significant cytotoxicity against the P388 murine leukemia cell line with an IC_{50} value of 0.092 µg/mL. In contrast, three new saponins and aginoside exhibited moderate activity at a concentration of 2.1 µg/mL on the same cell line (Sata et al. 1998). Other structurally-related saponins from *A. ampeloprasum* should also be investigated for their anticancer potential in order to develop a robust QSAR model which would assist in the development of novel anticancer drug candidates in the future.

7.4 *Allium fistulosum* L.

The acetone extract of *A. fistulosum* and its sulfide constituents at concentrations of 0-250 µg/mL exhibited significant dose-dependent anticancer activity by inhibiting the polarization of M2 activated macrophages, which suppressed tumor cell proliferation in mice osteosarcoma LM-8 cells (Nohara et al. 2017). In another assay, the methanol extract of *A. fistulosum* and its constituents viz. quercetin glycosides significantly inhibited growth in HepG2 cells while demonstrating less prominent inhibition in PC-3 and HT-29 cells (Pan et al. 2018). In another study, both the *n*-hexane and ethyl acetate extracts of *A. fistulosum* inhibited telomerase-mediated carcinogenicity at the concentration of 10 µg/mL. Both extracts of *A. fistulosum* suppressed the growth of gastric cancer cells (SNU-1) by 51.9% (IC_{50} value of 14.18 and 19.23 µg/mL, respectively) (Xu and Sung 2015). An extract of *A. fistulosum* also inhibited cell proliferation in the MDA-MB-453 cancer cell line and increased caspase-3 activity at a concentration of 100 µg/mL (Park HS et al. 2013).

Further studies on the anticancer potential of *A. fistulosum* are warranted. Such efforts should involve bioactivity-guided phytochemical screening of extracts and evaluation of the isolated compounds for anticancer activity. In depth intracellular analysis is also required to unravel the underlying mechanism leading to the cytotoxic effect of this species both *in vitro* and *in vivo*.

7.5 *Allium schoenoprasum* L.

In vivo assessment of aqueous and aqueous-ethanolic extracts of *A. schoenoprasum* leaves for potential anticancer properties was performed in male BDF mice (20–30 g) inoculated with Ehrlich carcinoma (EC) cells to develop solid tumors. Before tumor development, different groups of mice were treated orally with 1.3 g/kg body weight of both extracts for five days a week for a duration of 2.5 weeks. Following the grafting, the same process was continued throughout the study. The protective effect of extracts was measured by the volume and mass of tumors of the test groups compared to the grafted EC mice (control group). Both *A. schoenoprasum* extracts displayed moderate antitumor activity with tumor growth inhibitor (TGI) index values ranging from 10.2 to 38.4% (Shirshova TI et al. 2013).

Four spirostane-type glycosides and four steroidal saponins isolated from the whole plant of *A. schoenoprasum* were investigated *in vitro* against HCT-116 and HT-29 human colon cancer cell lines. All the tested phytochemicals exerted little to moderate cytotoxic activity against both cell lines. Both diosgenin 3-*O*-β-D-glucopyranosyl-(1→4)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranoside, and (25R)-furost-5-en-3β,22α,26- triol 26-*O*-β-D-glucopyranosyl-3-*O*-α-L-rhamnopyranosyl-(1→2)-[β-D-glucopyranosyl-(1→4)]-β-D-glucopyranoside demonstrated potent cytotoxicity against the HCT 116 cell line (IC_{50} values of 0.40 µM and 1.58 µM, respectively) and the HT-29 cell line (IC_{50} values of 0.75 µM and 1.56 µM, respectively). Only (25R)-5α-spirostan-3β,11α-diol-3-*O*-β-D-glucopyranosyl-(1→3)-[β-D-glucopyranosyl-(1→4)]-β-D-galactopyranoside was found to be moderately active (IC_{50} values of 8.45 µM and 8.64 µM against the HCT 116 and the HT-29 cell line, respectively. Another compound, laxogenin 3-*O*-α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranoside, proved to be ineffective against both cell lines with IC_{50} values greater than 100 µM (Timité et al. 2013).

Bioactive constituents from *A. schoenoprasum* have anticancer activity, but only against certain cell lines. Future efforts should be directed towards testing their effects on other cancer cell lines and on appropriate animal models with an emphasis on both selectivity and toxicity. The organosulfur compounds from this species are yet to be characterized with anticancer potential using valid scientific evidence. This warrants future investigations in order to evaluate their effects, both individually and collectively.

7.6 *Allium tuberosum* Rottler ex Spreng.

An extract of *A. tuberosum* at a concentration of 100 µg/mL was demonstrated to suppress cellular growth by 50.6% in the MDA-MB-453 cancer cell line. This was associated to its ability to up regulate the activity of caspase-3 (Park HS et al. 2013). Thiosulfinates isolated

from *A. tuberosum* were investigated in human colon cancer (HT-29) cells to evaluate their effect on apoptosis. They were found to initiate caspase-8-mediated Bid cleavage, which potentiated the action of caspase-9. This significantly reduced cell growth in a dose- and time-dependent manner, which was further associated with reduced levels of the anti-apoptotic (Bcl-2) protein, and elevated levels of the pro-apoptotic (Bax) protein. Thiosulfinates, at concentrations of 40 and 80 µg/mL, up-regulated the caspase-independent mitochondrial apoptosis factor (AIF) and stimulated DNA fragmentation as well as chromatin condensation in HT29 cells. In conclusion, these compounds were able to induce both the caspase-dependent and caspase-independent apoptotic pathways in HT-29 cells, leading to programmed cell death (Lee J-H et al. 2009). In another *in vitro* study, a new spirostanol saponin called tuberoside M isolated from the seeds of *A. tuberosum* exhibited potent suppression of human promyelocytic leukemia (HL-60) cells (IC_{50} value of 6.8 µg/mL) (Sang S-M et al. 2002).

Both the organosulfur and saponin constituents of *A. tuberosum* have been characterized with remarkable anticancer activity. This is in agreement with what has been demonstrated for the other *Allium* species under discussion. Additional studies are necessary to replicate these results in appropriate animal models in order to evaluate the selectivity and safety profiles of this species and its constituents. **Table 4** summarizes the potential of *Allium* vegetables in the management of cancer.

8. Toxicological profiles

Neither deaths nor any discernible gross pathological lesions were observed when the aqueous extract of *A. sativum* was administered to rabbits at doses of 300, 600, 1200 and 2200 mg/kg body weight. Only animals that were administered the extract at doses of 3200 and 4200 mg/kg body weight showed a slightly congested liver with confirmed death numbers. The median lethal dose (LD_{50}) was determined at 3034 mg/kg body weight (Mikail 2010). In acute toxicity studies, no death was recorded during the treatment period at all administered doses of the *A. sativum* extract. All animals were stable physiologically, with no evidence of toxicity with a dose up to 2500 mg/kg (Lawal et al. 2016). In oral acute toxicity tests in Swiss albino mice, the aqueous suspensions of both *A. sativum* and *A. cepa* bulbs, at the doses of 250 and 500 mg/kg exhibited no distinguishable signs of toxicity over a cumulative time-period of 24 hours. However, when administered at the higher dose of 25 g/kg, *A. sativum* altered respiration and heart rate while causing hyperthermia, reflex impairment, tremors, excitation, staggering, twitches, pilo-erection and itching in mice.

744 Similarly, *A. cepa* caused changes in heart rate and respiration, hypothermia, defecation and
745 pilo-erection at the dose of 30 g/kg. In chronic toxicity studies, female mice exhibited a
746 greater resistance to possible *A. sativum*-induced adverse effects over the ten week study
747 period compared to their male counterparts at the dose of 75 mg/kg/day. Nearing ten weeks,
748 female mice showed signs of mildly reduced heart rate and respiration as well as excitation,
749 itching and alopecia. In addition to these signs, the males further demonstrated aggression
750 starting in the 6th week. In case of *A. cepa*, a comparatively higher tolerance of the plant
751 material resulted in the experimentation to be conducted at the dose of 150 mg/kg/day for 12
752 weeks. Towards the end of that period, female mice exhibited mild hypothermia and itching
753 whereas the males demonstrated itching and alopecia in the 8th week of administration
754 (Alqasoumi et al. 2012). A regular diet for goats, containing up to 30% *A. cepa*, was
755 demonstrated to be safe (no clinical toxicity reported under the experimental conditions
756 used). Minor signs of clinical complications and marked hemolysis were reported when the
757 diet comprised of 60% *A. cepa*, thus limiting the excessive use of this species (Keyvanlou et
758 al. 2011). Both acute and chronic oral toxicity studies of the aqueous extract of *A.*
759 *ampeloprasum* were conducted in male and female Rockefeller mice. Administration of
760 single large doses of 1600, 6400 and 25600 mg/kg, followed by observation for 24 hours
761 showed no visible adverse reactions or effects. Daily administration of 2560 mg/kg extract
762 for seven days also failed to generate any signs of toxicity in either sexes, thus implying a
763 relative safety profile for this species upon oral intake (Barrientos, 2000). Animals treated
764 with *A. schoenoprasum* leaf extract at daily doses of 2000 mg/kg body weight did not exhibit
765 any sign of abnormal behavior, morbidity, or mortality till 14 days. This dose was reported as
766 the upper limit of daily administration (Singh, Krishan, et al. 2018).
767 Although many of the bioactive extracts aforementioned were of non- aqueous nature
768 and many individual bioactive phytoconstituents were isolated from such extracts, the
769 majority of the toxicity studies involved plant aqueous extracts. Therefore, future studies are
770 necessary to evaluate the toxicity potential of the non-aqueous extracts with respect to that of
771 the aqueous ones. The presence of the bioactive phytoconstituents should be ascertained
772 across different types of extracts to identify the best extraction method to be used in order to
773 recover high amounts of active constituents whilst retaining a good overall safety profile.
774
775 **9. Conclusion and future prospects**
776 *Allium* species have been used in a diverse range of cuisines around the world for centuries.
777 The six *Allium* species under discussion have been, and continue to be, employed as an

integral part of the human diet in many countries. A variety of conventional and non-conventional methodologies have been used for the manufacturing of *Allium*-derived food products, focusing extensively on the manufacturing of organosulfur compounds. Consequently, their use in the prevention and management of pathological conditions has greater prospects compared to other herbal remedies in terms of safety, availability and acceptance. *Allium* species are rich in volatile constituents, especially compounds of organosulfur origin. Such molecules have been characterized with significant anti-inflammatory and anticancer activity in both *A. sativum* and *A. cepa*. However, while the rest of the *Allium* species under discussion also feature similar organosulfur constituents in their volatile extracts, similar biological effects are yet to be characterized in favor of such constituents. Only selected organosulfur molecules from *A. tuberosum* have been demonstrated to exert anticancer properties. Therefore, future scientific endeavors should be directed towards these species so as to ascertain the anti-inflammatory and anticancer potential of their volatile constituents (both individually and collectively). Further biological testing of various structurally-related organosulfur compounds will advance the development of robust QSAR models which will accelerate the design and development of new medicines and dietary supplements. Saponins from *Allium* species present another potential source of novel bioactive molecules. A steroidal saponin from *A. ampeloprasum* was anti-inflammatory, whereas five saponins from *A. ampeloprasum*, four saponins from *Allium schoenoprasum* and one spirostanol saponin from *A. tuberosum* were characterized with prominent anticancer activity. The focus of further studies should be on saponins from other species of *Allium* and on the evaluation of their pharmacological potential. Comparative studies on the biological activity of both organosulfur and saponin constituents will undoubtedly be very informative.

Conflict of interests

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1171 **TABLES**

1172 **Table 1.** General information on the major *Allium* vegetables

Species	Accepted full name	Local / Common Names	Plant parts in use	Traditional uses	References
Allium sativum L.	*Allium sativum L.*	Garlic	Bulbs, leaves, and whole plants	Employed to heal abdominal discomfort, diarrhea, otitis media and respiratory tract infections in Nigeria.	(Fowotade et al. 2017)
				Used to prevent from common colds, hay fever and asthma in Europe and India.	(Fowotade et al. 2017)
				Used as an antimicrobial agent in Russia.	(Park HS et al. 2013)
			Whole plants	Used to cure deafness, ear aches, leprospy, flatulence, croup, whooping cough, tuberculosis, bronchoectasis and gangrene, and scurvy.	(Mikail 2010)
				Applied topically as a ruberfacient, vesicant, and anti-rheumatic agent.	(Mikail 2010)
			Bulbs	Used as a stimulant, carminative, antiseptic, anthelmintic, expectorant, diuretic, antisorbutic, aphrodisiac, and anti-asthmatic.	(Mikail 2010)
			Herb paste with honey	Used to alleviate rheumatic pain.	(Mikail 2010)
Allium cepa L.	*Allium cepa* L.	Bulb onion or Common onion	Bulbs, whole plants	Used to treat colds, influenza, cancer, snake bites, and hypertension.	(Han et al. 2013)
				Used as anthelmintic, aphrodisiac, carminative, emmenagogue, expectorant, tonic, and remedy against vertigo, migraine, bruises, bronchitis, cholera, colic, earache, fever, high blood pressure,	(Bora and Sharma 2009)

				diabetics, jaundice, pimples, dropsy and sores. Used to alleviate pain and swelling associated with bee or wasp stings.	
				Used for cancer, coronary heart disease, obesity, hypercholesterolemia, type 2 diabetes, hypertension, cataract, colic pain, flatulent colic, and dyspepsia.	(Corea et al. 2005)
Allium ampeloprasum L.	*Allium ampeloprasum* L.	Wild leek; Broadleaf wild leek; Sibujing (Philippines)	Powdered bulbs	For relieving symptoms associated with various inflammatory disorders, and for treating cough, mucous secretion, and sore throats in Brazil.	(Adão et al. 2011; Dey and Khaled 2015)
				The fresh juice of leek is taken orally to improve digestion.	(Dey and Khaled 2015)
			Whole plants	Used against fever, babies' teething discomfort, infections, and inflammation in the Phillipines.	(Añides et al. 2019)
				Employed as an antihelmintic, diuretic, antihypertensive, and for digestive disorders.	(García-Herrera et al. 2014)
Allium fistulosum L	*Allium fistulosum* L.	Welsh onion; Bunching onion; Long green onion; Japanese bunching onion; Asian leek; Spring onion	Bulbs, leaves and whole plants	Effective in the treatment of the common cold, arthritis, and headaches.	(Jafarian et al. 2007; Zolfaghari et al. 2021)
Allium schoenoprasum L.	*Allium schoenoprasum* L.	Chives; Snow Mountain Garlic; Kashmiri garlic	Leaves and whole plants	Used for hypertension, digestive problems, colds, flu and lung congestion, pain from sunburn and sore throat.	(Singh, Chauhan, et al. 2018)
Allium tuberosum	*Allium tuberosum*	Garlic chive;	Leaves	In Chinese folk medicine, used to treat impotence	(Sang S et al.

L.	Rottler ex Spreng.	Jiucai (China); Nira (Japan); Chinese chives (English); Kuchai (Malaysia); Kucai (Indonesia); Kutsay; Ganda (Philippines); Kuichai (Thailand); Maroi-nakuppi (Manipur, North East India)		and nocturnal emissions, abdominal pain, diarrhea, hematemesis, snakebite, and asthma.	2001; Hu et al. 2006; Lee J-H et al. 2009)
			Seeds	Used in Chinese medicine as a tonic and aphrodisiac.	(Hu et al. 2006)
			Whole plants	A decoction is used for the prevention of liver and gastrointestinal disorders, and to lower glucose and cholesterol serum levels.	(Jannat et al. 2019b)
			Whole plants	Tonic and booster of the digestive and immune systems, as well as an antidote for snake bites and poisonous bee or wasp stings.	(Jannat et al. 2019b)
			Roots	Employed for gastric ulcers and dyspepsia.	(Jannat et al. 2019b)
			Whole plants	Used for various ailments such as kidney, liver and digestive disorders, anemia, and fatigue.	(Li Q-M et al. 2018) (Jannat et al. 2019b)
			Whole plants	A poultice is applied to relieve fever. Also used to treat asthma (Philippines)	(Jannat et al. 2019b)

				Used to heal spermatorrhoea in India	(Jannat et al. 2019b)
				As a mouthwash to soothe toothaches in Thailand and the Indo-chinese region.	(Jannat et al. 2019b)

1188 **Table 2.** Phytochemical constituents from the major *Allium* vegetables

No.	Compounds	Sources	Plant part(s)	References
Volatile constituents (organosulphur compounds)				
1	Dipropyl monosulfide	*A. sativum*	Bulbs	(Mikail 2010); (Martins et al. 2016)
2	Methyl allyl sulfide	*A. sativum*	Bulbs	(Mikail 2010); (Martins et al. 2016)
3	Diallyl sulphide	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
4	Dimethyl disulfide	*A. tuberosum*	Aerial parts	(Jannat et al. 2019a)
		A. schoenoprasum	Leaves	(Singh, Chauhan, et al. 2018)
5	Methyl-propyldisulphide	*A. schoenoprasum*	Leaves	(Block 1992; Singh, Chauhan, et al. 2018)
6	Pentyl hydrodisulfide	*A. schoenoprasum*	Leaves	(Block 1992; Singh, Chauhan, et al. 2018)
7	Methyl pentyldisulfide	*A. schoenoprasum*	Leaves	(Block 1992; Singh, Chauhan, et al. 2018)
8	Dipropyl disulphide	*A. schoenoprasum*	Leaves	(Block 1992; Singh, Chauhan, et al. 2018)
		A. cepa	Bulbs	(Teshika et al. 2019)
		A. sativum	Bulbs	(Mikail 2010; Martins et al. 2016)
9	Methyl-1-propenyl disulphide	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
		A. tuberosum	Aerial parts	(Jannat et al. 2019a)
10	Allyl methyl disulfide/ Methyl-2-propenyl disulfide	*A. tuberosum*	Aerial parts	(Jannat et al. 2019a)
		A. sativum	Bulbs	(Martins et al. 2016)
		A. cepa	Bulbs	(Teshika et al. 2019)
11	1-propenyl propyl disulphide/ Cis-propenyl propyl disulfide	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)

		A. cepa	Bulbs	(Teshika et al. 2019)
12	Trans-propenyl propyl disulfide	*A. cepa*	Bulbs	(Teshika et al. 2019)
13	Allyl propyl disulphide	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
14	Diallyl disulfide	*A. tuberosum*	Aerial parts	(Jannat et al. 2019a)
		A. sativum	Bulbs	(Mikail 2010; Martins et al. 2016)
15	Methyl-1-(methylthio) ethyl disulphide	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
16	Methyl -1-(methylthiopropyl) disulphide	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
17	Dimethyl trisulfide	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
		A. tuberosum	Aerial parts	(Jannat et al. 2019a)
18	Methyl propyl trisulfide	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
		A. cepa	Bulbs	(Teshika et al. 2019)
19	Dipropyl trisulfide	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
		A. cepa	Bulbs	(Teshika et al. 2019)
		A. sativum	Bulbs	(Mikail 2010; Martins et al. 2016)
20	Methyl-1-propenyl trisulfide	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
21	Allyl methyl trisulfide	*A. tuberosum*	Aerial parts	(Jannat et al. 2019a)
		A. schoenoprasum	Leaves	(Singh, Chauhan, et al. 2018)
22	Diallyl trisulfide (DATS)	*A. sativum*	Bulbs	(Martins et al. 2016)
23	Di-1-propenyl trisulfide	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)

24	Dimethyl tetrasulfide	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
		A. ampeloprasum	Bulbs	(Añides et al. 2019)
25	Dipropyl tetrasulfide	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
		A. sativum	Bulbs	(Mikail 2010; Martins et al. 2016)
26	Allicin	*A. sativum*	Bulbs	(Martins et al. 2016)
		A. cepa	Bulbs	(Zamri and Abd Hamid 2019)
27	S-allyl cysteine	*A. sativum*	Bulbs	(Martins et al. 2016)
		A. cepa	Bulbs	(Zamri and Abd Hamid 2019)
28	S-allyl cysteine sulfoxide	*A. sativum*	Bulbs	(Martins et al. 2016)
		A. cepa	Bulbs	(Teshika et al. 2019)
29	S- allylmercaptocysteine	*A. cepa*	Bulbs	(Zamri and Abd Hamid 2019)
30	2-Vinyl-4H-1,3-dithiin	*A. sativum*	Bulbs	(Martins et al. 2016)
31	1,2-vinyldithiin	*A. sativum*	Bulbs	(Martins et al. 2016)
32	Allixin	*A. sativum*	Bulbs	(Martins et al. 2016)
33	Xanthiazone	*A. cepa*	Bulbs	(Zamri and Abd Hamid 2019)
		A. ampeloprasum	Bulbs	(Zamri and Abd Hamid 2019)
34	Xanthiside	*A. cepa*	Bulbs	(Zamri and Abd Hamid 2019)
		A. ampeloprasum	Bulbs	(Zamri and Abd Hamid 2019)
35	2-Hydroxyxanthiside	*A. cepa*	Bulbs	(Zamri and Abd Hamid 2019)
		A. ampeloprasum	Bulbs	(Zamri and Abd Hamid 2019)
36	Entadamide A-β-D-	*A. cepa*	Bulbs	(Zamri and Abd Hamid 2019)

	glucopyranoside	*A. ampeloprasum*	Bulbs	(Zamri and Abd Hamid 2019)
37	Glucoerucin	*A. cepa*	Bulbs	(Zamri and Abd Hamid 2019)
38	Onionin A1	*A. cepa*	Bulbs	(Nohara et al. 2017)
		A. fistulosum	Bulbs	(Nohara et al. 2017)
39	Onionin A2	*A. cepa*	Bulbs	(Nohara et al. 2017)
		A. fistulosum	Bulbs	(Nohara et al. 2017)
40	Onionin A3	*A. cepa*	Bulbs	(Nohara et al. 2017)
		A. fistulosum	Bulbs	(Nohara et al. 2017)
41	Garlicnin B1	*A. sativum*	Bulbs	(Nohara et al. 2017)
42	Garlicnin B2	*A. sativum*	Bulbs	(Nohara et al. 2017)
43	Garlicnin B3	*A. sativum*	Bulbs	(Nohara et al. 2017)
44	Garlicnin B4	*A. sativum*	Bulbs	(Nohara et al. 2017)
45	Garlicnin K1	*A. sativum*	Bulbs	(Nohara et al. 2017)
46	Garlicnin K2	*A. sativum*	Bulbs	(Nohara et al. 2017)
47	Garlicnin C1	*A. sativum*	Bulbs	(Nohara et al. 2017)
48	Garlicnin C2	*A. sativum*	Bulbs	(Nohara et al. 2017)
49	Garlicnin C3	*A. sativum*	Bulbs	(Nohara et al. 2017)
50	Garlicnin A	*A. sativum*	Bulbs	(Nohara et al. 2017)
51	Garlicnin I	*A. sativum*	Bulbs	(Nohara et al. 2017)
52	Welsonin A1	*A. fistulosum*	Bulbs	(Nohara et al. 2017)
53	Welsonin A2	*A. fistulosum*	Bulbs	(Nohara et al. 2017)

54	Garlicnin J	*A. sativum*	Bulbs	(Nohara et al. 2017)
55	Garlicnin G	*A. sativum*	Bulbs	(Nohara et al. 2017)
56	Garlicnin L-1	*A. sativum*	Bulbs	(Nohara et al. 2017)
57	Garlicnin L-2	*A. sativum*	Bulbs	(Nohara et al. 2017)
58	Garlicnin L-3	*A. sativum*	Bulbs	(Nohara et al. 2017)
59	Garlicnin L-4	*A. sativum*	Bulbs	(Nohara et al. 2017)
60	E-Ajoene	*A. sativum*	Bulbs	(Martins et al. 2016)
		A. cepa	Bulbs	(Zamri and Abd Hamid 2019)
		A. ampeloprasum	Bulbs	(Zamri and Abd Hamid 2019)
61	Z-Ajoene	*A. sativum*	Bulbs	(Martins et al. 2016)
62	Garlicnin E	*A. sativum*	Bulbs	(Nohara et al. 2017)
63	Garlicnin F	*A. sativum*	Bulbs	(Nohara et al. 2017)
Volatile constituents (non-organosulphur compounds)				
64	2-methyl-2-pentenal	*A. schoenoprasum*	Leaves	(Block 1992; Singh, Chauhan, et al. 2018)
65	2-methyl-2-butenal	*A. schoenoprasum*	Leaves	(Block 1992; Singh, Chauhan, et al. 2018)
66	Trans-2-Ethyl-3- methylthiophane	*A. ampeloprasum*	Bulbs	(Añides et al. 2019)
67	(Z)-1-(Methylthio)-1- propene	*A. ampeloprasum*	Bulbs	(Añides et al. 2019)
68	Dichloroacetic acid	*A. fistulosum*	Leaves	(Ajayi et al. 2019)
69	1-Buten-3-yne, 1- chloro-, (Z)-	*A. fistulosum*	Leaves	(Ajayi et al. 2019)
70	3-Ethyl-3-heptanol	*A. ampeloprasum*	Bulbs	(Añides et al. 2019)
71	Nonane	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)

72	*n*-Pentadecane	*A. ampeloprasum*	Bulbs	(Añides et al. 2019)
73	*n*-Hexadecane	*A. ampeloprasum*	Bulbs	(Añides et al. 2019)
74	4,6-dimethyldodecane	*A. ampeloprasum*	Bulbs	(Añides et al. 2019)
75	α-farnesene	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
76	*E*-Beta farnesene	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
77	*n*-Heptadecane	*A. ampeloprasum*	Bulbs	(Añides et al. 2019)
78	*n*-Octadecane	*A. ampeloprasum*	Bulbs	(Añides et al. 2019)
79	*n*-Eicosane	*A. ampeloprasum*	Bulbs	(Añides et al. 2019)
80	*n*- Heneicosane	*A. ampeloprasum*	Bulbs	(Añides et al. 2019)
81	Hexadecenoic acid, ethyl ester	*A. ampeloprasum*	Bulbs	(Añides et al. 2019)
82	Octadecanoic acid, ethyl ester	*A. ampeloprasum*	Bulbs	(Añides et al. 2019)
83	Linoleic acid, ethyl ester	*A. ampeloprasum*	Bulbs	(Añides et al. 2019)
84	Borneol	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
85	*p*-Menth-8(10)-ene-2,9-diol	*A. ampeloprasum*	Bulbs	(Añides et al. 2019)
86	1-Isopropyl-1,2-cyclohexanediol/ 1,2-Cyclohexanediol, 1-(1-methylethyl)- cis-	*A. ampeloprasum*	Bulbs	(Añides et al. 2019)
87	D-Limonene	*A. fistulosum*	Leaves	(Ajayi et al. 2019)
88	α-Pinene	*A. fistulosum*	Leaves	(Ajayi et al. 2019)
89	Sesquiphellandrene	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
90	Thymol	*A. fistulosum*	Leaves	(Ajayi et al. 2019)

91	Phenol, 2,4-bis (1,1-dimethylethyl)-	*A. ampeloprasum*	Bulbs	(Añides et al. 2019)
92	α-copaene	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
93	Caryophyllene	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
Saponins				
94	Tuberoside A	*A. tuberosum*	Seeds	(Sang S et al. 1999; Jannat et al. 2019a)
95	Tuberoside B	*A. tuberosum*	Seeds	(Sang S et al. 1999; Jannat et al. 2019a)
96	Tuberoside C	*A. tuberosum*	Seeds	(Sang S et al. 1999; Jannat et al. 2019a)
97	Tuberoside D	*A. tuberosum*	Seeds	(Jannat et al. 2019b)
98	Tuberoside E	*A. tuberosum*	Seeds	(Jannat et al. 2019b)
99	Tuberoside F	*A. tuberosum*	Seeds	(Jannat et al. 2019b)
100	Tuberoside G	*A. tuberosum*	Seeds	(Jannat et al. 2019b)
101	Tuberoside H	*A. tuberosum*	Seeds	(Jannat et al. 2019b)
102	Tuberoside I	*A. tuberosum*	Seeds	(Jannat et al. 2019b)
103	Tuberoside J	*A. tuberosum*	Seeds	(Jannat et al. 2019b)
104	Tuberoside K	*A. tuberosum*	Seeds	(Jannat et al. 2019b)
105	Tuberoside L	*A. tuberosum*	Seeds	(Jannat et al. 2019b)
106	Tuberoside M	*A. tuberosum*	Seeds	(Jannat et al. 2019b)
107	Tuberoside N	*A. tuberosum*	Seeds	(Jannat et al. 2019b)
108	Tuberoside O	*A. tuberosum*	Seeds	(Jannat et al. 2019b)
109	Tuberoside P	*A. tuberosum*	Seeds	(Jannat et al. 2019b)

110	Tuberoside Q	*A. tuberosum*	Seeds	(Jannat et al. 2019b)
111	Tuberoside R	*A. tuberosum*	Seeds	(Jannat et al. 2019b)
112	Tuberoside S	*A. tuberosum*	Seeds	(Jannat et al. 2019b)
113	Tuberoside T	*A. tuberosum*	Seeds	(Jannat et al. 2019b)
114	Tuberoside U	*A. tuberosum*	Seeds	(Jannat et al. 2019b)
115	Ascalonicoside A1	*A. cepa*	Whole plants	(Corea et al. 2005)
116	Ascalonicoside A2	*A. cepa*	Whole plants	(Corea et al. 2005)
117	Ascalonicoside B	*A. cepa*	Whole plants	(Corea et al. 2005)
118	Yayoisaponin A	*A. ampeloprasum*	Whole plants	(Sata et al. 1998)
119	Yayoisaponin B	*A. ampeloprasum*	Whole plants	(Sata et al. 1998)
120	Yayoisaponin C	*A. ampeloprasum*	Whole plants	(Sata et al. 1998)
121	Aginoside	*A. ampeloprasum*	Whole plants	(Sata et al. 1998)
122	Tropeoside A1	*A. cepa*	Whole plants	(Corea et al. 2005)
123	22-*O*-methyl derivative of Tropeoside A1	*A. cepa*	Whole plants	(Corea et al. 2005)
124	Tropeoside B1	*A. cepa*	Whole plants	(Corea et al. 2005)
125	22-*O*-methyl derivative of Tropeoside B1	*A. cepa*	Whole plants	(Corea et al. 2005)
126	Tropeoside A2	*A. cepa*	Whole plants	(Corea et al. 2005)
127	22-*O*-methyl derivative of Tropeoside A2	*A. cepa*	Whole plants	(Corea et al. 2005)

128	Tropeoside B2	*A. cepa*	Whole plants	(Corea et al. 2005)
129	22-*O*-methyl derivative of Tropeoside B2	*A. cepa*	Whole plants	(Corea et al. 2005)
130	Dioscin	*A. ampeloprasum*	Whole plants	(Sata et al. 1998)
131	Tuberosine A [(25S)-5β-spirostan-2β,3β-diol 3-*O*-β-D-glucopyranoside]	*A. tuberosum*	Roots	(Jannat et al. 2019b)
132	Tuberosine B [(25S)-5β-spirostan 2β,3β,19-triol 3-*O*-β-D-glucopyranoside]	*A. tuberosum*	Roots	(Jannat et al. 2019b)
133	Tuberosine C [(25S)-5β-spirostan-2β,3β-diol 3-*O*-α-L-rhamnopyranoyl-(1- 4)-*O*-β-D-glucopyranoside]	*A. tuberosum*	Roots	(Jannat et al. 2019b)
134	(3β,5α,6β,25R)-6-[(β-D-glucopyranosyl)oxy]-spirostan-3-yl *O*-β-D-glucopyranosyl-(1→2)-*O*-[β-D-glucopyranosyl-(1→3)]-β-D-galactopyranoside	*A. ampeloprasum*	Bulbs	(Adão et al. 2011)
135	(20S,25S)-spirost-5-en-3β,12β,21-triol 3-*O*-α-L-rhamnopyranosyl-(1–	*A. schoenoprasum*	Whole plants	(Timité et al. 2013)

	2)-β-D-glucopyranoside			
136	(20S,25S)-spirost-5-en-3β,11α,21-triol 3-*O*-α-L-rhamnopyranosyl-(1–2)-β-D-glucopyranoside	*A. schoenoprasum*	Whole plants	(Timité et al. 2013)
137	Laxogenin 3-*O*-α-L-rhamnopyranosyl-(1–2)-[β-D-glucopyranosyl-(1–4)]-β-D-glucopyranoside	*A. schoenoprasum*	Whole plants	(Timité et al. 2013)
138	Laxogenin-3-*O*-α-L-rhamnopyranosyl-(1–2)-β-D-glucopyranoside	*A. schoenoprasum*	Whole plants	(Timité et al. 2013)
139	Diosgenin-3-*O*-α-L-rhamnopyranosyl-(1–2)-*O*-β-D-glucopyranoside (Prosapogenin A of dioscin)	*A. schoenoprasum*	Whole plants	(Timité et al. 2013)
140	Diosgenin-3-*O*-β-D-glucopyranosyl-(1–4)-[α-L-rhamnopyranosyl-(1–2)]-β-D-glucopyranoside (deltonin)	*A. schoenoprasum*	Whole plants	(Timité et al. 2013)
141	(25R)-5α -spirostan-3β,11α -diol3-*O*-β-D-glucopyranosyl-(1–3)-[β-D	*A. schoenoprasum*	Whole plants	(Timité et al. 2013)

	glucopyranosyl-(1–4)]-β-D-galactopyranoside			
142	(25R)-furost-5-en-3β,22α,26-triol 26-*O*-β-D-glucopyranosyl-3-*O*-α-L-rhamnopyranosyl- (1–2)-[β-D-glucopyranosyl-(1–4)]-β-D-glucopyranoside (deltoside)	*A. schoenoprasum*	Whole plants	(Timité et al. 2013)
143	26-*O*-β-D-glucopyranosyl- (25R)-3β,22x,26-trihydroxyl-5α-furostane3-*O*-bchacotrioside	*A. tuberosum*	Seeds	(Jannat et al. 2019a)
144	26-*O*-β-D-glucopyranosyl- (25S)-3β,5β,6α,22x,26-pentahydroxyl-5β-furostane 3-*O*-α-L-rhamnopyranosyl-(1→4)-β-D-glucopyranoside	*A. tuberosum*	Seeds	(Jannat et al. 2019a)
145	3-*O*-α-L-rhamnopyranosyl-(1→4)-β-D-glucopyranosyl 3β,5β,6α,16β-tetrahydroxypregnane 16-(5-*O*-β-D-glucopyranoyl-4(S)-methyl-5-hydroxypentanoic acid) ester	*A. tuberosum*	Seeds	(Jannat et al. 2019a)
Flavonoids				

146	Kaempferol	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
		A. fistulosum		(Vlase et al. 2013)
		A. ampeloprasum	Seeds and leaves	(Abd and Ali 2013)
		A. cepa	Stems	(Corea et al. 2005)
147	Quercetin	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
		A. sativum	Bulbs	(Martins et al. 2016)
		A. cepa	Stems	(Corea et al. 2005; Teshika et al. 2019) (Fredotović Ž et al. 2017)
		A. ampeloprasum	Seeds and leaves	(Abd and Ali 2013)
		A. fistulosum		(Vlase et al. 2013)
148	Myricetin	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
		A. cepa		(Fredotović Ž et al. 2017)
149	Luteolin	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
150	Isorhamnetin	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
		A. cepa	Whole plants	(Fredotović Ž et al. 2017)
151	Naringenin	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
152	Taxifolin	*A. cepa*	Bulbs	(Corea et al. 2005)
153	Isoquercetin	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018); (Teshika et al. 2019)
		A. fistulosum	Whole plants	(Vlase et al. 2013)
154	Quercitrin	*A. fistulosum*	Whole plants	(Vlase et al. 2013)

155	Rutin	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
156	Kaempferol 3-*O*-β-sophoroside	*A. tuberosum*	Aerial parts	(Jannat et al. 2019a)
157	Kaempferol 3,4-*O*-di-*O*-β-D-glucoside	*A. tuberosum*	Aerial parts	(Jannat et al. 2019a)
158	Astragalin/ Kaempferol 3-β-D-glucoside	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
159	Isorhamnetin 3-β-D-glucoside	*A. schoenoprasum*	Leaves	(Singh, Chauhan, et al. 2018)
160	Isorhamnetin 3-*O*-galactopyranoside	*A. fistulosum*		(Zolfaghari et al. 2021)
161	Spiraeoside/ Quercetin-4′-monoglucoside	*A. cepa*	Stems	(Fredotović Ž et al. 2017; Teshika et al. 2019)
162	Quercetin-3, 4′-diglucoside	*A. cepa*	Stems	(Fredotović Ž et al. 2017; Teshika et al. 2019)
163	Quercetin-7,4′-diglucoside	*A. cepa*	Stems	(Teshika et al. 2019)
164	Isorhamnetin-3,4’-diglucoside	*A. cepa*	Stems	(Teshika et al. 2019)
165	Quercetin-3,7,4′-triglucoside	*A. cepa*	Stems	(Teshika et al. 2019)
166	Taxifolin 7-glucoside	*A. cepa*	Bulbs	(Corea et al. 2005)
167	Delphinidin-3,5-diglucoside	*A. cepa*	Stems	(Teshika et al. 2019)
168	3-*O*-β-D-(2-*O*-feruloyl)-glucosyl-7, 40-di-*O*-β-D-glucosylkaempferol	*A. tuberosum*	Aerial parts	(Jannat et al. 2019a)
169	3-*O*-β-sophorosyl-7-*O*-β-D-(2-*O*-feruloyl) glucosyl kaempferol	*A. tuberosum*	Aerial parts	(Jannat et al. 2019a)

Anthocyanins				
170	Cyanidin 3-(6-malonylglucoside)	*A. schoenoprasum*	Flowers and stem	(Fossen et al. 2000; Singh, Chauhan, et al. 2018)
		A. sativum	Leaves	(Phan et al. 2019)
171	Cyanidin 3-(3-malonylglucoside)	*A. schoenoprasum*	Flowers and stem	(Fossen et al. 2000; Singh, Chauhan, et al. 2018)
172	Cyanidin-3-*O*-glucoside	*A. schoenoprasum*	Flowers and stem	(Fossen et al. 2000; Singh, Chauhan, et al. 2018)
173	Peonidin-3′-glucoside	*A. cepa*	Bulbs	(Fredotović Ž et al. 2017; Teshika et al. 2019)
174	Malvidin-3′-glucoside	*A. cepa*	Bulbs	(Fredotović Ž et al. 2017; Teshika et al. 2019)
Phenolic compounds				
175	Protocatechuic acid	*A. cepa*	Stems	(Teshika et al. 2019)
176	Vanillic acid	*A. ampeloprasum*	Seeds and leaves	(Abd and Ali 2013)
177	Gallic acid	*A. schoenoprasum*	Roots, stalk and leaves	(Parvu AE et al. 2014); (Singh, Chauhan, et al. 2018)
		A. cepa	Stems	(Teshika et al. 2019)
		A. ampeloprasum	Seeds and leaves	(Abd and Ali 2013)
178	*p*-coumaric acid	*A. schoenoprasum*	Roots, stalk and leaves	(Parvu AE et al. 2014); (Singh, Chauhan, et al. 2018)
		A. fistulosum	Whole plants	(Vlase et al. 2013)
		A. ampeloprasum	Seeds and leaves	(Abd and Ali 2013)

179	Caffeic acid	*A. ampeloprasum*	Seeds and leaves	(Abd and Ali 2013)
180	Ferulic acid	*A. schoenoprasum*	Roots, stalk and leaves	(Parvu AE et al. 2014); (Singh, Chauhan, et al. 2018)
		A. fistulosum	Whole plants	(Vlase et al. 2013)
		A. cepa	Stems	(Teshika et al. 2019)
181	Sinapic acid	*A. schoenoprasum*	Roots, stalk and leaves	(Parvu AE et al. 2014); (Singh, Chauhan, et al. 2018)
		A. fistulosum	Whole plants	(Vlase et al. 2013)
182	*N*-coumaroyltyramine	*A. fistulosum*	Whole plants	(Zolfaghari et al. 2020)
183	Moupinamide/ *N*-feruloyl tyramine	*A. ampeloprasum*	Seeds and stems	(Sadeghi et al. 2013)
		A. fistulosum	Whole plants	(Zolfaghari et al. 2020)
184	*N*-caffeoyl tyramine	*A. ampeloprasum*	Seeds and stems	(Sadeghi et al. 2013)
		A. fistulosum	Whole plant	(Zolfaghari et al. 2020)
185	*N*-coumaroyltyrosine	*A. fistulosum*	Whole plant	(Zolfaghari et al. 2020)
186	Persicoimidate	*A. ampeloprasum*	Seeds and stems	(Sadeghi et al. 2013)
		A. fistulosum	Whole plants	(Zolfaghari et al. 2020)
187	Fistuloimidate A	*A. fistulosum*	Whole plants	(Zolfaghari et al. 2020)
188	Fistuloimidate B	*A. fistulosum*	Whole plants	(Zolfaghari et al. 2020)
189	Chlorogenic acid	*A. cepa*	Stems	(Teshika et al. 2019)
		A. ampeloprasum	Seeds and leaves	(Abd and Ali 2013)
190	Tuberonoid A	*A. tuberosum*	Aerial parts	(Jannat et al. 2019a)

191	Tuberonoid B	*A. tuberosum*	Aerial parts	(Jannat et al. 2019a)
192	Tuberosine D	*A. tuberosum*	Roots	(Jannat et al. 2019a)
193	(7R, 8S)-dihydrodehydrodiconiferyl alcohol-di-9, 90-*O*-β-D-glucopyranoside	*A. tuberosum*	Whole plants	(Jannat et al. 2019a)
Organic acids and fatty acids				
194	Oxalic acid	*A. cepa*	Stems	(Teshika et al. 2019)
195	Succinic acid	*A. cepa*	Stems	(Teshika et al. 2019)
196	Malic acid	*A. cepa*	Stems	(Teshika et al. 2019)
197	Tartaric acid	*A. cepa*	Stems	(Teshika et al. 2019)
198	Citric acid	*A. cepa*	Stems	(Teshika et al. 2019)
199	Ascorbic acid	*A. cepa*	Stems	(Teshika et al. 2019)
200	Palmitic acid	*A. schoenoprasum*	Leaves	(Shirshova T et al. 2013; Singh, Chauhan, et al. 2018)
201	Linoleic acid	*A. schoenoprasum*	Leaves	(Shirshova T et al. 2013; Singh, Chauhan, et al. 2018)
		A. tuberosum	Seeds	(Hu et al. 2006)
		A. tuberosum	Seeds	(Hu et al. 2006)
202	Linolenic acid	*A. schoenoprasum*	Leaves	(Shirshova T et al. 2013; Singh, Chauhan, et al. 2018)
203	Oleic acid	*A. tuberosum*	Seeds	(Hu et al. 2006)

204	Stearic acid	*A. tuberosum*	Seeds	(Hu et al. 2006)
205	Arachidic acid	*A. tuberosum*	Seeds	(Hu et al. 2006)
206	Docosanoic acid/ Behenic acid	*A. tuberosum*	Seeds	(Hu et al. 2006)
207	Tricosanoic acid	*A. tuberosum*	Seeds	(Hu et al. 2006)
208	Tetracosanoic acid/ Lignoceric acid	*A. tuberosum*	Seeds	(Hu et al. 2006)
Steroids				
209	Sitosterol	*A. schoenoprasum*	Whole plants	(Shirshova T et al. 2013; Singh, Chauhan, et al. 2018)
		A. fistulosum	Whole plants	(Vlase et al. 2013)
210	Stigmasterol	*A. schoenoprasum*	Whole plants	(Shirshova T et al. 2013; Singh, Chauhan, et al. 2018)
		A. fistulosum	Whole plants	(Vlase et al. 2013)
211	Cholesterol	*A. schoenoprasum*	Whole plants	(Shirshova T et al. 2013)
212	Campesterol	*A. schoenoprasum*	Whole plants	(Shirshova T et al. 2013; Singh, Chauhan, et al. 2018)
		A. fistulosum	Whole plants	(Vlase et al. 2013)
Amino acids				
213	Tryptophan	*A. schoenoprasum*	Whole plants	(Singh, Chauhan, et al. 2018)
		A. tuberosum	Seeds	(Hu et al. 2006)
214	Threonine	*A. schoenoprasum*	Whole plants	(Singh, Chauhan, et al. 2018)
		A. tuberosum	Seeds	(Hu et al. 2006)

215	Leucine	*A. schoenoprasum*	Whole plants	(Singh, Chauhan, et al. 2018)
		A. tuberosum	Seeds	(Hu et al. 2006)
216	Isoleucine	*A. schoenoprasum*	Whole plants	(Singh, Chauhan, et al. 2018)
		A. tuberosum	Seeds	(Hu et al. 2006)
217	Lysine	*A. schoenoprasum*	Whole plants	(Singh, Chauhan, et al. 2018)
218	Methionine	*A. schoenoprasum*	Whole plants	(Singh, Chauhan, et al. 2018)
		A. tuberosum	Seeds	(Hu et al. 2006)
219	Phenylalanine	*A. schoenoprasum*	Whole plants	(Singh, Chauhan, et al. 2018)
		A. tuberosum	Seeds	(Hu et al. 2006)
220	Tyrosine	*A. schoenoprasum*	Whole plants	(Singh, Chauhan, et al. 2018)
		A. tuberosum	Seeds	(Hu et al. 2006)
221	Valine	*A. schoenoprasum*	Whole plants	(Singh, Chauhan, et al. 2018)
		A. tuberosum	Seeds	(Hu et al. 2006)
222	Alanine	*A. tuberosum*	Seeds	(Hu et al. 2006)
223	Histidine	*A. schoenoprasum*	Whole plants	(Singh, Chauhan, et al. 2018)
		A. tuberosum	Seeds	(Hu et al. 2006)
224	Aspartic acid	*A. schoenoprasum*	Whole plants	(Singh, Chauhan, et al. 2018)
		A. tuberosum	Seeds	(Hu et al. 2006)
225	Glutamic acid	*A. schoenoprasum*	Whole plants	(Singh, Chauhan, et al. 2018)
		A. tuberosum	Seeds	(Hu et al. 2006)
226	Cystine	*A. tuberosum*	Seeds	(Hu et al. 2006)

227	Arginine	*A. schoenoprasum*	Whole plants	(Singh, Chauhan, et al. 2018)
		A. tuberosum	Seeds	(Hu et al. 2006)
228	Glycine	*A. schoenoprasum*	Whole plants	(Singh, Chauhan, et al. 2018)
		A. tuberosum	Seeds	(Hu et al. 2006)
229	Proline	*A. schoenoprasum*	Whole plants	(Singh, Chauhan, et al. 2018)
		A. tuberosum	Seeds	(Hu et al. 2006)
230	Serine	*A. schoenoprasum*	Whole plants	(Singh, Chauhan, et al. 2018)
Glutamyl peptides				
231	γ-Glutamyl-S-methyl-L-cysteine	*A. sativum*	Whole plants	(Martins et al. 2016)
		A. cepa	Whole plants	(Bora and Sharma 2009)
232	γ-Glutamyl-methionine	*A. cepa*	Whole plants	(Bora and Sharma 2009)
233	γ-Glutamyl-isoleucine	*A. cepa*	Whole plants	(Bora and Sharma 2009)
234	γ-Glutamyl-valine	*A. cepa*	Whole plants	(Bora and Sharma 2009)
235	γ-Glutamyl-leucine	*A. cepa*	Whole plants	(Bora and Sharma 2009)
236	γ-Glutamylphenylalanine	*A. cepa*	Whole plants	(Bora and Sharma 2009)
237	γ-Glutamyl-tyrosine	*A. cepa*	Whole plants	(Bora and Sharma 2009)
238	γ-Glutamyl-S-methyl-L-cysteine sulfoxide	*A. cepa*	Whole plants	(Bora and Sharma 2009)
239	γ -Glutamyl-S-*trans*-(1-propenyl)-L-cysteine- sulfoxide	*A. cepa*	Whole plants	(Bora and Sharma 2009)
240	Glutathione	*A. cepa*	Whole plants	

241	γ-Glutamyl-S-(2-carboxypropyl)-cysteinylglycine	*A. cepa*	Whole plants	(Bora and Sharma 2009)
242	Cysteine-glutathione disulfide	*A. cepa*	Whole plants	(Bora and Sharma 2009)
Vitamins				
243	Thiamin	*A. tuberosum*	Seeds	(Hu et al. 2006)
		A. schoenoprasum	Whole plants	(Singh, Chauhan, et al. 2018)
244	Riboflavin	*A. tuberosum*	Seeds	(Hu et al. 2006)
		A. schoenoprasum	Whole plants	(Singh, Chauhan, et al. 2018)
245	Vitamin C	*A. sativum*	Whole plants	(Martins et al. 2016)
		A. schoenoprasum	Whole plants	(Singh, Chauhan, et al. 2018)
246	Pantothenic acid	*A. schoenoprasum*	Whole plants	(Singh, Chauhan, et al. 2018)
247	Vitamin B complex	*A. sativum*	Whole plants	(Martins et al. 2016)
		A. schoenoprasum	Whole plants	(Singh, Chauhan, et al. 2018)
248	Vitamin B6	*A. schoenoprasum*	Whole plants	(Singh, Chauhan, et al. 2018)
249	Niacin	*A. tuberosum*	Seeds	(Hu et al. 2006)
250	Vitamin A	*A. schoenoprasum*	Whole plants	(Singh, Chauhan, et al. 2018)
251	Vitamin E	*A. schoenoprasum*	Whole plants	(Singh, Chauhan, et al. 2018)
252	Vitamin K	*A. schoenoprasum*	Whole plants	(Singh, Chauhan, et al. 2018)
253	β-carotene	*A. schoenoprasum*	Whole plants	(Singh, Chauhan, et al. 2018)
Nucleosides				
254	Thymine	*A. tuberosum*	Roots	(Jannat et al. 2019b)

255	Adenine	*A. tuberosum*	Roots	(Jannat et al. 2019b)
256	Uridine	*A. tuberosum*	Roots	(Jannat et al. 2019b)
257	Thymidine	*A. tuberosum*	Roots	(Jannat et al. 2019b)
258	Guanosine	*A. tuberosum*	Roots	(Jannat et al. 2019b)
259	Adenosine	*A. tuberosum*	Roots	(Jannat et al. 2019b)
260	Deoxyadenosine	*A. tuberosum*	Roots	(Jannat et al. 2019b)

1204 **Table 3.** Anti-inflammatory activity of the major *Allium* vegetables

Species	Tested material	Testing method	Doses administered	Biological effects	References
***In vitro* studies**					
A. sativum	Aged black garlic extract	RAW 264.7 cells	25 µg/mL	Anti-inflammatory via decreasing levels of NO, IL-6, and TNF-α.	(You et al. 2019)
	Chloroform and methanol extracts of aged black garlic	RAW 264.7 cells	250 µg/mL	Strong anti-inflammatory activity.	(Jeong et al. 2016)
	Allicin	Human T cells and human umbilical vein endothelial cells (HUVEC)	20-100 µM	Reduced chemokine-induced and VLA-4-mediated T cell functions.	(Sela et al. 2004)
	Alliin	3T3-L1 adipocytes	100 µM	Anti-inflammatory activity via downregulating the gene expression of pro-inflammatory cytokines.	(Quintero-Fabián et al. 2013)
	Quercetin	RAW 264.7 cells	0.1 and 0.2 mM	Inhibited the transcription process of inducible nitric oxide synthase (iNOS).	(Wadsworth and Koop 1999)

	Garlic extract and S-allyl cysteine	RAW 264.7 cells	N/A	Modulating NO production.	(Kim K-M et al. 2001)
	Diallyl disulfide	RAW 264.7 cells	200 µg/mL	Reduced pro-inflammatory cytokines and NO levels.	(Shin et al. 2013)
	Dimethylsulfoxide extract of garlic powder	Human embryonic kidney cells (HEK293)	100 µg/mL	Modulation of cytokines in human blood and suppression of NF-κB activity in the surrounding tissue.	(Keiss et al. 2003a)
A. cepa	Hot water extract	RAW 264.7 cells	0.1-100 µg/mL	Reduced NO, IL-6, IL-1β, and TNF-α production.	(Kang B-K et al. 2015)
A. cepa	Diphenyl thiosulfinate, thiosulfinates and cepaenes	Human granulocytes	0.1–100 µM	Exerted prominent anti-inflammatory activity.	(Dorsch et al. 1990)
A. ampeloprasum	Ethanol extract	Human mast cells (HMC-1)	1.0 mg/mL	Reduced TNF-α and IL-6 levels.	(Ko et al. 2013b)
A. fistulosum	Aqeuous extract	RAW 264.7 cells	66 µg/mL	Noticeably reduced NO production.	(Tsai et al. 2005)
	Aqueous and ethanol extracts (whole plants and roots)	BV2 microglia cells	50 µg/mL	Strongly down regulated the translation process of various pro-inflammatory cytokines.	(Park S-H et al. 2011b)
A. tuberosum	Ethanol extract	Human umbilical vein	100 µg/mL	Exerted potent anti-	(Hur and Lee

		endothelial cells (HUVECs)		inflammatory action through reduction of the expression of adhesion molecules.	2017)
***In vivo* studies in experimental animal models**					
A. sativum	Allicin	Male Wistar albino rats/ carrageenan induced paw edema in rats	250 mg/kg body weight	Potent anti-inflammatory activity.	(Bose et al. 2013)
	Aged black garlic extract	Swiss CD-1 mice	0.5 mg/mL	Exterd significant anti-dermatitic activity.	(You et al. 2019)
	Diallyl sulfide (DAS)	Wistar rats	200 mg/kg daily	Showed potent anti-inflammatory activity.	(Abdel-Daim et al. 2020)
	Thymoquinone (TQ)	Wistar rats	10 mg/kg daily	Strong anti-inflammatory activity.	(Abdel-Daim et al. 2020)
A. cepa	Ethanol extract	RAW 264.7 cells and mice ear edema	100 μg/mL	Diminished the production of NO, IL-6, TNF−α, and IL-1β, as well as the expression of COX-2, iNOS, NF−κB, and MAPKs in a dose-dependent fashion.	(Ahn et al. 2015)
	Hot water extract	ICR mice/ croton oil-induced ear edema	250 mg/kg	Exerted prominent anti-inflammatory action.	(Kang B-K et al. 2015)
	Methanol extract	A/J mice	10, 100, and	Suppressed the secretion of pro-	(Oliveira et al.

			1000 µg/mL	inflammatory cytokines.	2015b)
	Quercetin	A/J mice	3.75, 7.5, and 15 µg/mL	Inhibited the secretion of pro-inflammatory cytokines.	(Oliveira et al. 2015b)
A. ampeloprasum	(3*β*,5*α*,6*β*,25*R*)-6-[(*β*-D-glucopyranosyl)oxy]-spirostan-3-yl *O*-*β*-d-glucopyranosyl-(1→2)-*O*-[*β*-D-glucopyranosyl-(1→3)]-*β*-d-galactopyranoside	Male Swiss mice/ carrageenan-induced edema	100 mg/kg	Demonstrated potent anti-inflammatory activity.	(Adão et al. 2011)
A. fistulosum	Aqueous extract	Mice/ carrageenan induced edema	0.25, 0.5, and 1 g/kg	Exhibited dose-dependent inhibition on the paw edema.	(Wang B-S et al. 2013)
A. fistulosum	75% methanol- water and chloroform extracts (bulbs)	Balb/c male mice	1-1000 mg/kg	Notedly reduced the paw edema thickness at 100 and 1000 mg/kg.	(Jafarian et al. 2007)
A. schoenoprasum	70% ethanol extract (leaves)	Wistar-Bratislava albino rats/ turpentine oil induced inflammation	5 mL/kg body weight	Inhibited phagocytosis and diminished oxidative stress.	(Parvu A et al. 2014)
A. tuberosum	Polysaccharides	Kunming male mice	200 mg/kg daily	Suppressed the production of pro-inflammatory cytokines.	(Li Q-M et al. 2018)

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1206 **Table 4** Anticancer activity of the major *Allium* vegetables

Species	**Tested material**	**Testing method**	**Doses administered**	**Biological effects**	**References**
***In vitro* studies**					
A. sativum	Garlic oil	human promyelocytic leukemia (HL-60) cells	20 µg/mL	Strong antiproliferative effect.	(Seki et al. 2000)
	Low temperature (LG) and UMPM (UG) extracts	RAW 264.7 and fibrosarcoma (HT-1080) cell lines	125, 250, 500, and 1000 µg/mL	Remarkable cytotoxicity and NO inhibition.	(Kim H-J et al. 2010)
	Diallyl sulfide	Rat hepatocytes	0.5 and 2 mM	Decreased DNA damage through up-regulating the activity of GST and glutathione peroxidase (GPx).	(Sheen et al. 2001)
	Diallyl disulfide	Rat hepatocytes	0.5 and 1 mM	Reduced DNA damage through up-regulating the activity of GST and glutathione peroxidase (GPx).	(Sheen et al. 2001)
	Hydro-alcoholic extract of bulbs	MCF-7, A549 and PA-1 cancer cells	0.01, 0.1, 10 and 100 µg/ mL	Prominent antiproliferative activity.	(Nema et al. 2014)

	Diallyl sulfide (DAS), Diallyl disulfide (DADS) and Diallyl trisulfide (DATS)	HCT-15 cell line	N/A	IC_{50} value of >100 µM, >100 µM and 5.0 ± 0.2 µM, respectively.	(Yang et al. 2001)
	Diallyl disulfide	HCT-15 (colon), A549 (lung), SK MEL-2 (skin) cancer cells.	100 and 500 µM	Inhibited cell proliferation.	(Sundaram and Milner 1996)
	Diallyl disulfide (DADS) and Diallyl trisulfide (DATS)	HL-60, HCT-15 (colon), A549 (lung), SK MEL-2 (skin), and prostate cancer cells.	N/A	Anticancer effect mediated via cell cycle arrest, growth inhibition, differentiation, apoptosis, and potentiation of the immune system.	(Ariga and Seki 2006)
	Diallyl trisulfide (DATS)	Human colon adenocarcinoma (HCT-15 and DLD-1) cells.	N/A	Increased caspase-3-mediated apoptosis.	(Hosono et al. 2005)
	Garlic oil	human promyelocytic leukemia (HL-60) cells	20 µg/mL	Strong antiproliferative effect.	(Seki et al. 2000)
A. cepa	Hexane and ethyl acetate extracts	Human gastric adenocarcinoma cells	20 µg/mL	Significant anti-proliferative activity.	(Xu and Sung 2015)

		(SNU-1)			
	70% methanol water extract	DNA Nicking and Comet Assays	10–100 µg/mL	Potent DNA protective action.	(Fredotović Ž et al. 2017)
		Breast cancer (MDA-MB-231) and human glioblastoma cells (A1235)	100 µg/mL	Higher anti-proliferative effect on glioblastoma cells than breast cancer cells.	(Fredotović Ž et al. 2017)
	Ethyl acetate extract	MDA-MB-231 cells	0-250 µg/ mL	Stimulation of apoptosis via reduction of fatty acid synthase (FAS) activity.	(Wang Y et al. 2012b)
		U937, THP-1, and K562 human leukemic cells, and Raw 246.7 mouse macrophages	60 µg/ mL	Suppressed cancer cell proliferation through inducing caspase-dependent apoptosis.	(Han et al. 2013)
		Human AGS cells	50 µg/ mL	Inhibition of cancer cell growth.through up regulation of p53 expression, and subsequent Bax induction, altering Bcl-2 protein.	(Han et al. 2013)
	Cepa2	P3U1 myeloma cancer cells	N/A	Inhibited P3U1 cell growth.	(Abd and Ali 2013;

					Abdelrahman et al. 2017a)
	Quercetin 3-*O*-β-D-glucoside	HepG2, HT-29 and PC-3 cancer cells	1 mg/mL	Moderate anti-proliferative effect.	(Pan et al. 2018)
A. cepa and *A. fistulosum*	Onionin A1	Human monocyte-derived macrophages / cell enzyme-linked immunosorbent assay (Cell-ELISA) and mouse osteosarcoma LM-8 cells	100 µg/mL	Suppressed tumor proliferation mediated by macrophage activation.	(Nohara et al. 2017)
	Quercetin-3,4'-di-*O*-glucoside	HepG2, HT-29 and PC-3 cancer cells	1 mg/mL	Strong anti-proliferative activity.	(Pan et al. 2018)
	Quercetin-4'-*O*-glucoside	HepG2, HT-29 and PC-3 cancer cells	1 mg/mL	Potent cytotoxicity.	(Pan et al. 2018)
A. ampeloprasum	Extract	Osteosarcoma cell line (U2OS)	N/A	Prohibited cancer cell proliferation and the development of metastasis.	(Dey and Khaled 2015)
	Ethanol, methanol and aqueous extracts	MCF-7 human breast cancer cells	50 µg/mL	Effectively inhibited cell growth.	(Zamri and Abd Hamid 2019)

	Yayoisaponins A-C	P388 cells	2.1 µg/mL	Showed significant cytotoxicity.	(Sata et al. 1998)
	Aginoside	P388 cells	2.1 µg/mL	Showed significant cytotoxicity.	(Sata et al. 1998)
A. fistulosum	Hexane extract	Human acute promyeloid leukemic cells (HL-60) / Telomeric repeat amplification protocol-PCR (TRAP-PCR) assay	10 µg/mL	Strong telomerase inhibitory effect.	(Xu and Sung 2015)
		MDA-MB-453 cancer cells	100 µg/mL	Antiproliferative activity.	(Park HS et al. 2013)
A. schoenoprasum	Diosgenin 3-*O*-β-D-glucopyranosyl-(1→ 4)-[α-L-rhamnopyranosyl-(1→2)]-β-D-glucopyranoside (deltonin)	HCT 116 and HT-29 human colon cancer cells	0.1% v/v in DMSO	Remarkable cytotoxicity.	(Timité et al. 2013)
	(25R)-furost-5-en-3β,22α,26- triol 26-*O*-β-	HCT 116 and HT-29 human colon cancer	0.1% v/v in DMSO	Prominent cytotoxicity.	(Timité et al. 2013)

	D-glucopyranosyl-3-*O*-α-L-rhamnopyranosyl-(1→2)- [β-D-glucopyranosyl-(1→4)]-β-D-glucopyranoside (deltoside)	cells			
A. tuberosum	Thiosulfinates	HT-29 human colon cancer cells	10 g/mL, 20 g/mL, 40 g/mL, and 80 g/mL	Antiproliferative effect mediated by both the caspase-dependent and caspase-independent apoptotic pathways.	(Lee J-H et al. 2009)
	Extract	Breast cancer MDA-MB-453 cancer cells	100 µg/ mL	Suppressed cells proliferation through controlling caspase-3 activity.	(Park HS et al. 2013)
	Tuberoside M	Human promyelocytic leukemia cells (HL-60)	1, 10, 100 µg/mL	Strong cytotoxicity (IC50 value of 6.8 µg/mL).	(Sang S-M et al. 2002)
***In vivo* studies in experimental animal models**					
A. sativum	Diallyl sulfide and diallyl disulfide	SPF Wistar rats	1 mmol/kg	Prominent antitumor action via modulating metabolites of aflatoxin B1.	(Guyonnet et al. 2002)
	Z-ajoene	Sarcoma 180 and hepatocarcinoma cells	N/A	Exhibited anti tumor effect.	(Ariga and Seki 2006)

		treated mice			
A. cepa and *A. fistulosum*	Onionin A1	Osteosarcoma (LM-8)-bearing C3H mice and ovarian cancer (iMOC)-bearing C57B6 mice	20 mg/kg	Inhibited tumor develoment and metastasis in experimental animals.	(Nohara et al. 2017)
A. schoenoprasum	Aqueous and aqueous-ethanol extracts of leaves	Male BDF mice	1.3g/kg (p.o.)	Suppressed the growth of subcutaneously grafted Ehrlich carcinoma cells at the tumor development stage.	(Shirshova T et al. 2013)

FIGURES LEGENDS

Figure 1. Organosulfur volatile constituents from major *Allium* vegetables

Figure 2. Non-organosulfur volatile constituents from major *Allium* vegetables

Figure 3. Saponins from major *Allium* vegetables

Figure 4. Flavonoids, flavonoids glycosides and anthocyanins from major *Allium* vegetables

Figure 5. Phenolic constituents from major *Allium* vegetables

Figure 6. Organic acids and fatty acids from major *Allium* vegetables

Figure 7. Steroidal compounds from major *Allium* vegetables

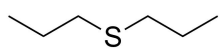
Figure 8. Amino acids from major *Allium* vegetables

Figure 9. Vitamins and nucleosides from major *Allium* vegetables

Figure 10. Anti-inflammatory mode of actions of selected *Allium* vegetables and their individual phytoconstituents

Figure 11. Schematic representation of the anticancer effects of PLAC on a cellular model

Figure 1 Part 1



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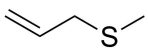

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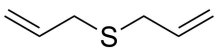

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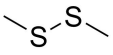

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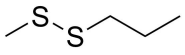

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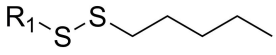
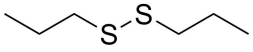


6 R_1= H
7 R_1= CH_3



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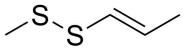

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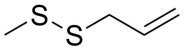

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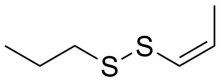

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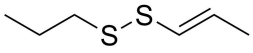

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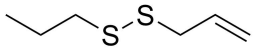

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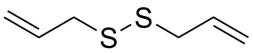

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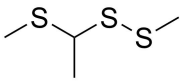

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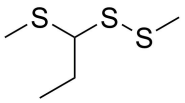

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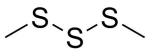

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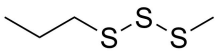

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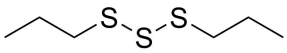

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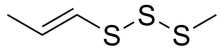

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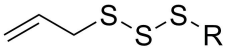
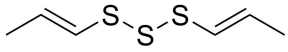


21 R_1= CH_3
22 R_1= CH_2-CH=CH_2



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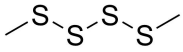

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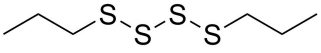

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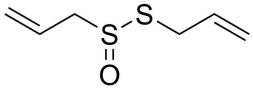

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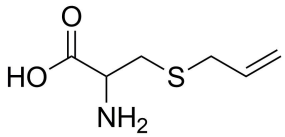

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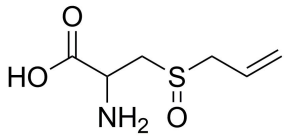

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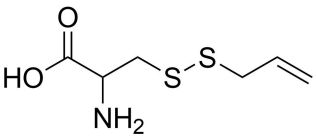

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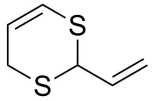

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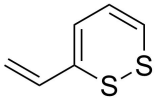

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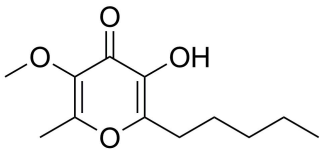

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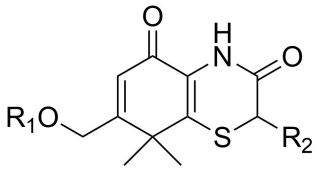
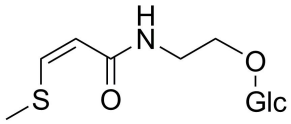


33 R_1=R_2= H
34 R_1= Glc, R_2= H
35 R_1= Glc, R_2= OH



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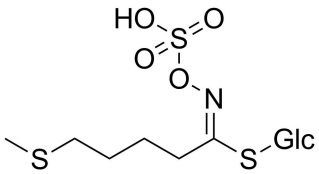

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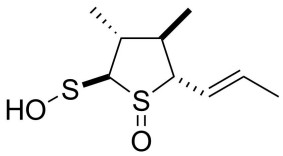

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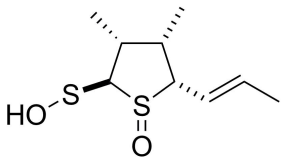

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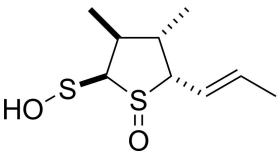

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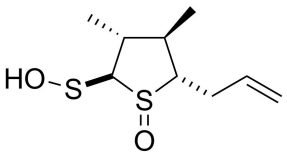

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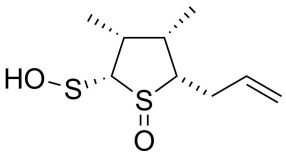

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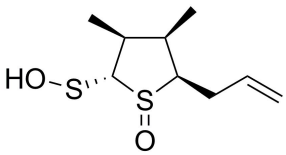

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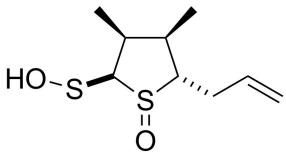

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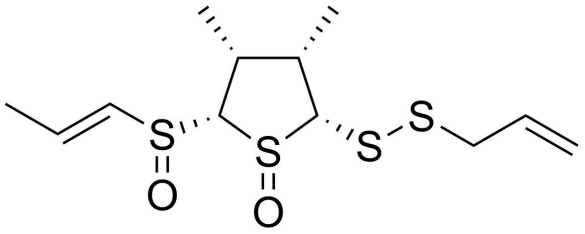
Figure 1 Part 2



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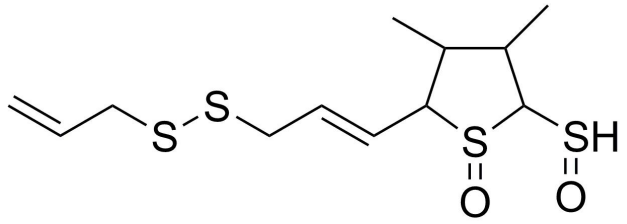

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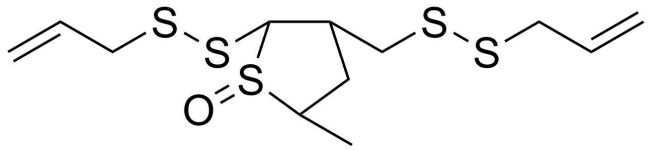

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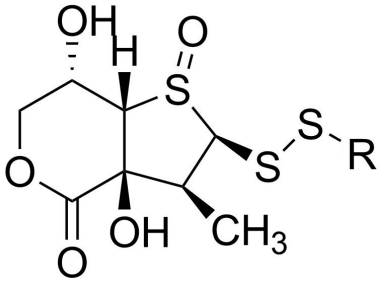
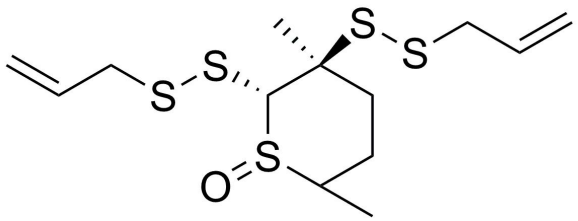


52 R= CH=CHCH3
53 R= CH3



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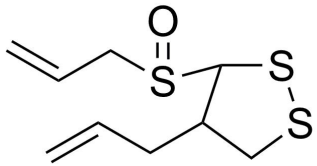

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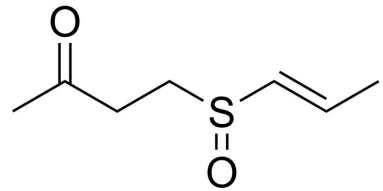

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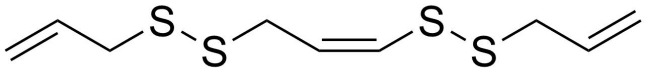

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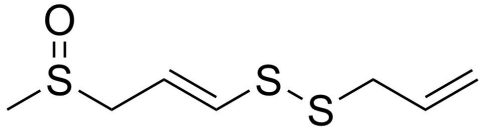

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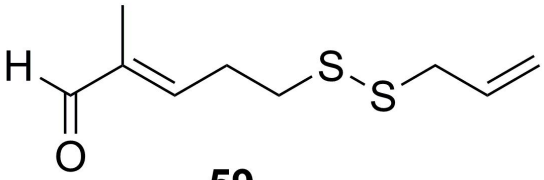

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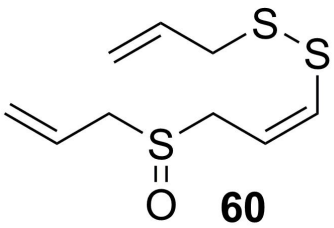

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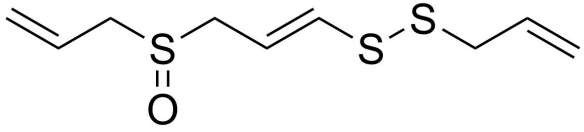

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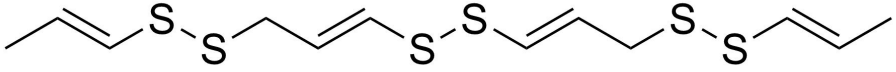

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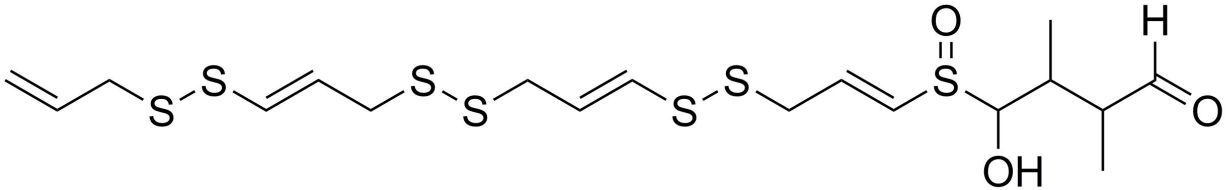

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Figure 2

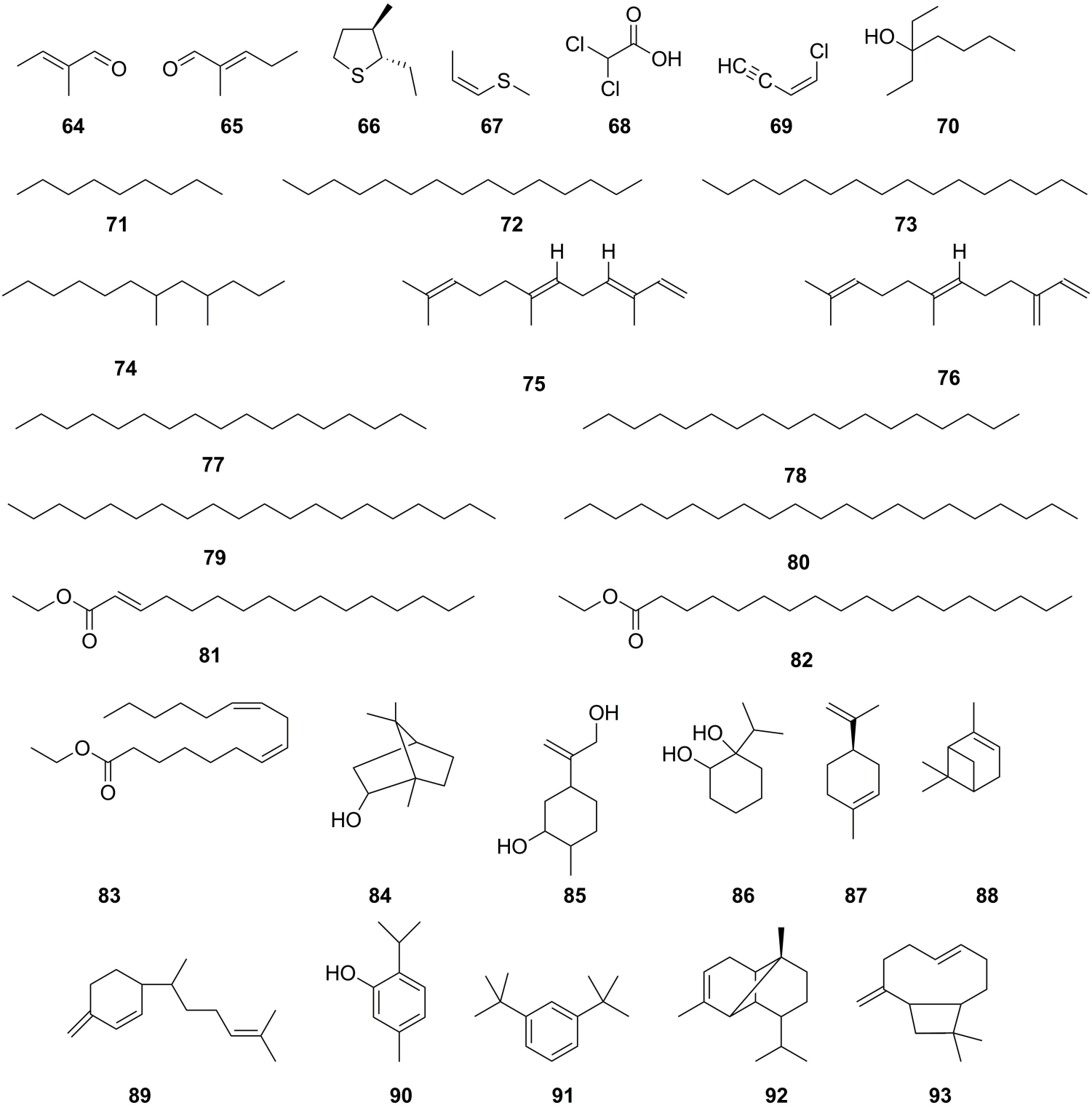
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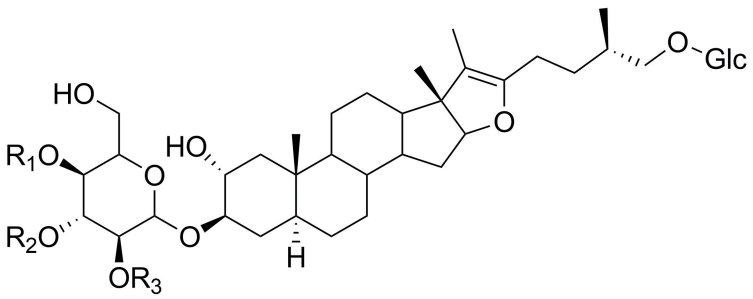
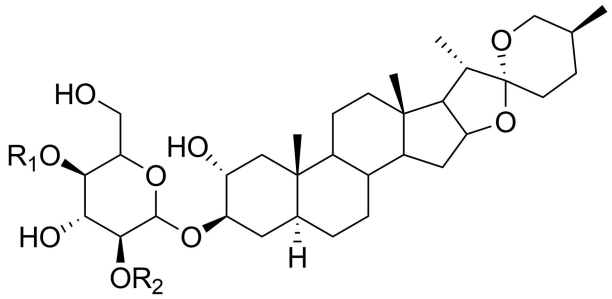
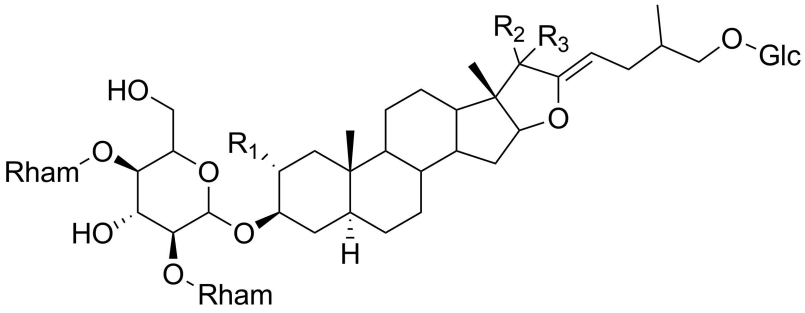
Figure 3 Part 1



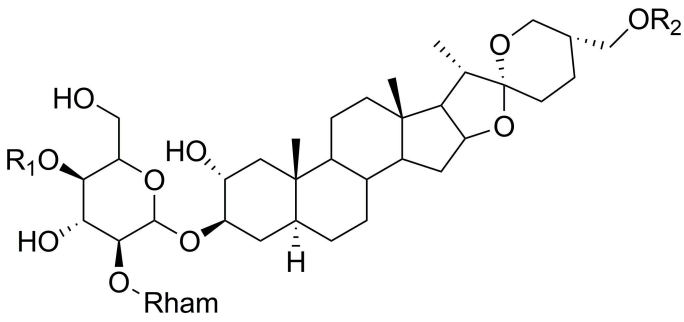
94 R_1=R_2= H, R_3= Rham
95 R_1=Rham, R_2= H, R_3= Rham
96 R_1= H, R_2= Glc, R_3= Rham



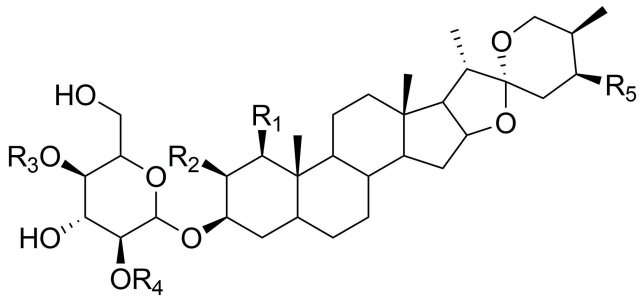
97 R_1=R_2=Rham
98 R_1=Rham, R_2= Glc



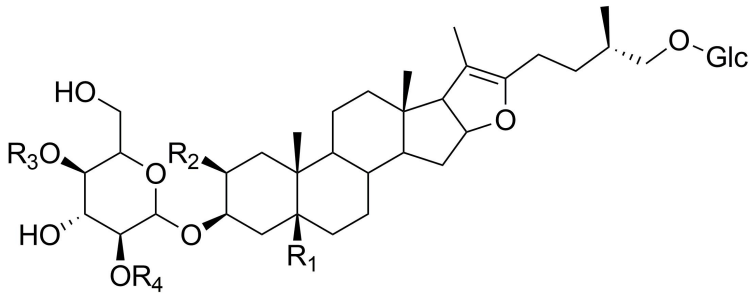
99 R_1= OH, R_2= Me, R_3= OMe
100 R_1=R_3=OH, R_2= Me
101 R_1=R_2=OH, R_3= Me
102 R_1= H, R_2=OH, R_3= Me



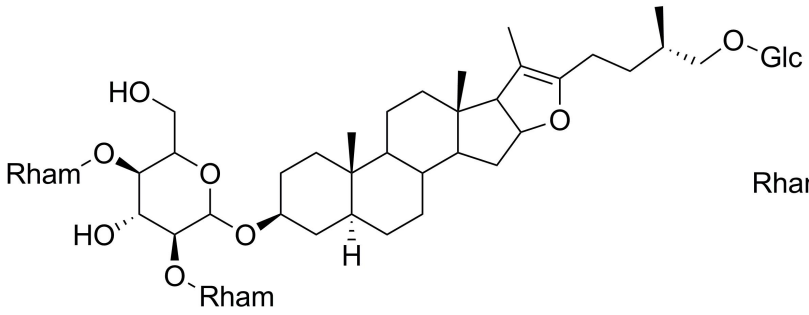
103 R_1=R_2= H
104 R_1= Rham, R_2= H
105 R_1= Rham, R_2= Glc



106 R_1= OH, R_2=R_4=R_5= H, R_3= Rham
107 R_1=R_5= H, R_2= OH, R_3= Rham, R_4= Glc
108 R_1=R_3=R_4=R_5= H, R_2= OH
109 R_1=R_4=R_5= H, R_2= OH, R_3= Rham
110 R_1=R_4= H, R_2=R_5= OH, R_3= Rham



111 R_1=R_2= OH, R_3=R_4= H
112 R_1=R_2= H, R_3= Rham, R_4= Glc



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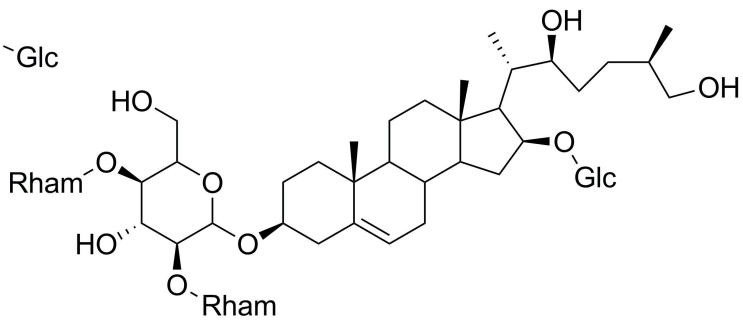
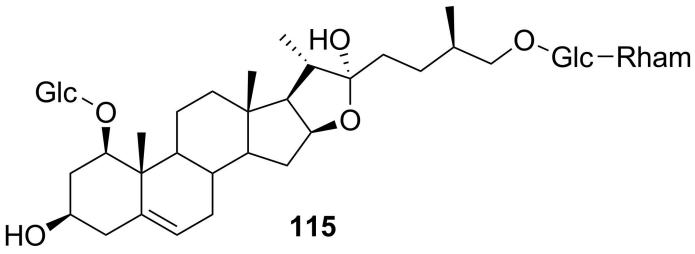


114

Figure 3 Part 2



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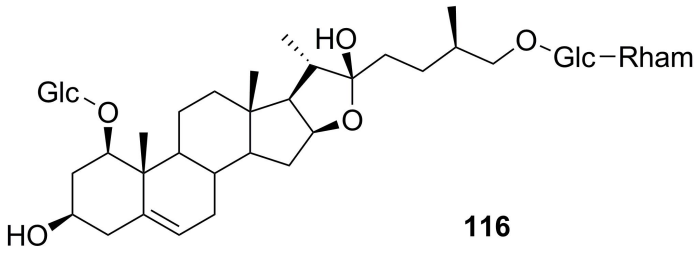

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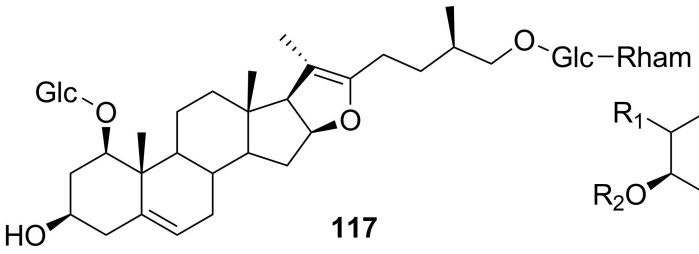

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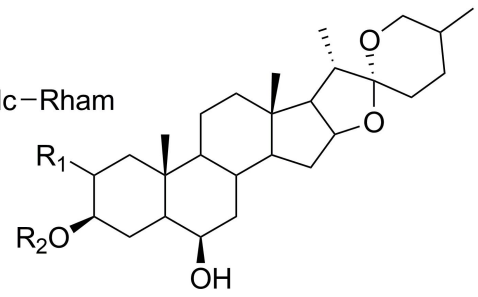
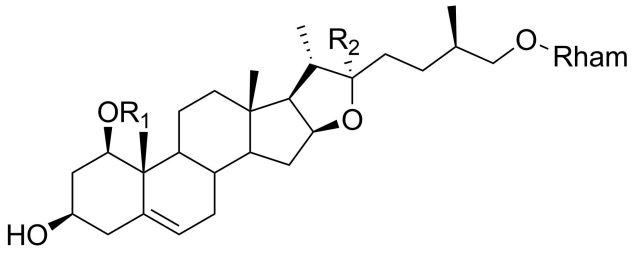


118 R_1= OH, R_2= Gal-Glc-Xyl
|
Glc-Glc

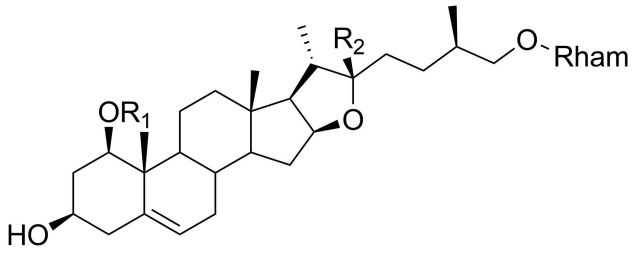
119 R_1= =O, R_2= Gal-Glc-Xyl
|
Glc-Glc

120 R_1= OH, R_2= Gal-Glc-Glc
|
Glc

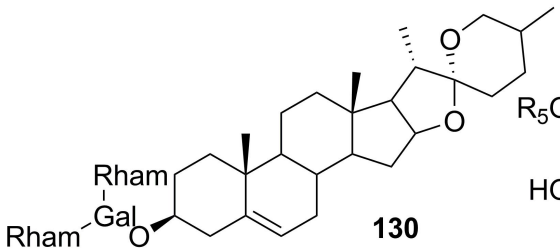
121 R_1= OH, R_2= Gal-Glc-Xyl
|
Glc



122 R_1= Gal, R_2= OH
123 R_1= Gal, R_2= OCH_3
124 R_1= Xyl, R_2= OH
125 R_1= Xyl, R_2= OCH_3



126 R_1= Gal, R_2= OH
127 R_1= Gal, R_2= OCH_3
128 R_1= Xyl, R_2= OH
129 R_1= Xyl, R_2= OCH_3



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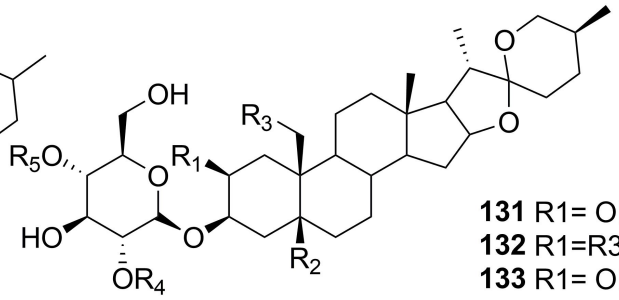
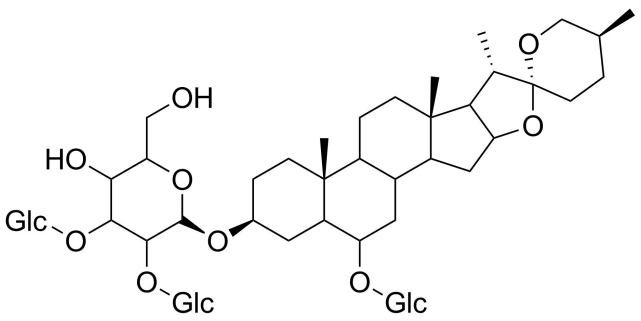
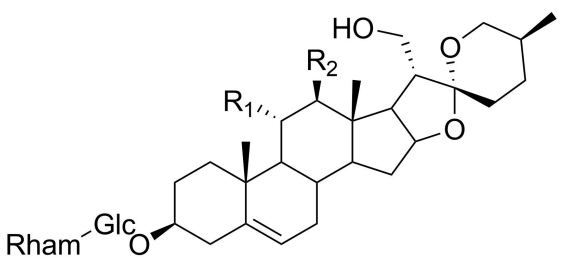


131 R1= OH, R2=R3=R4=R5= H
132 R1=R3= OH, R2=R4=R5= H
133 R1= OH, R2=R3=R4= H, R5= Rham

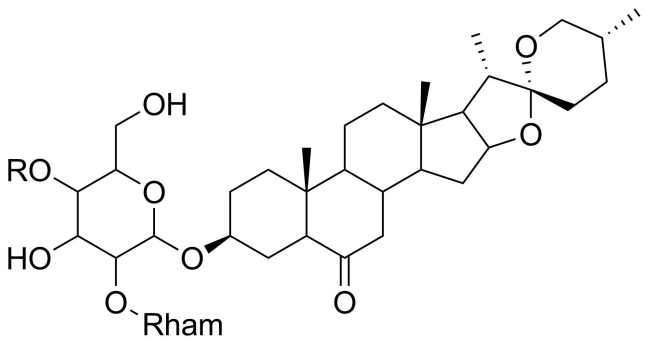


134

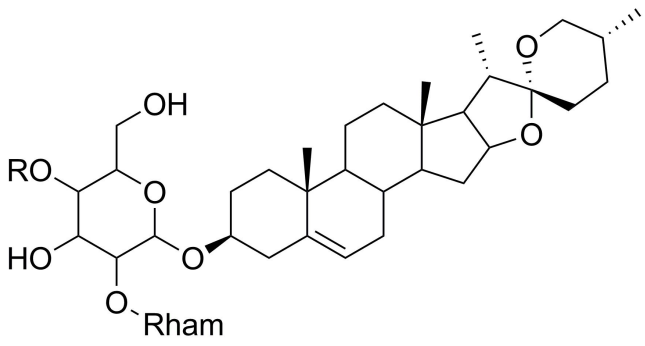


135 R_1= H, R_2= OH
136 R_1= OH, R_2= H

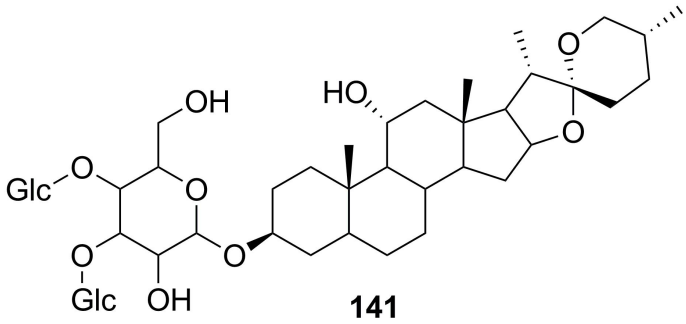
Figure 3 Part 3



137 R= Glc
138 R= H



139 R= H
140 R= Glc



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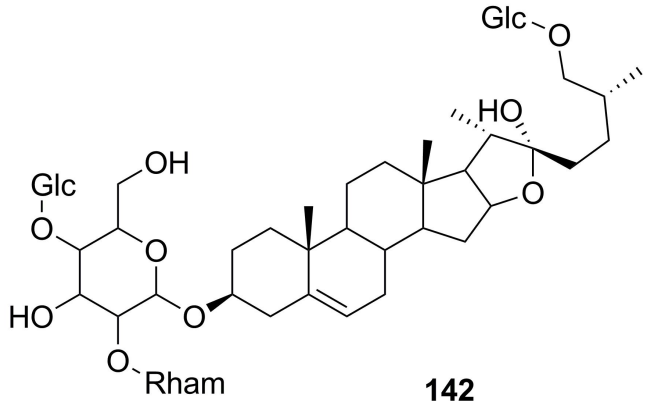

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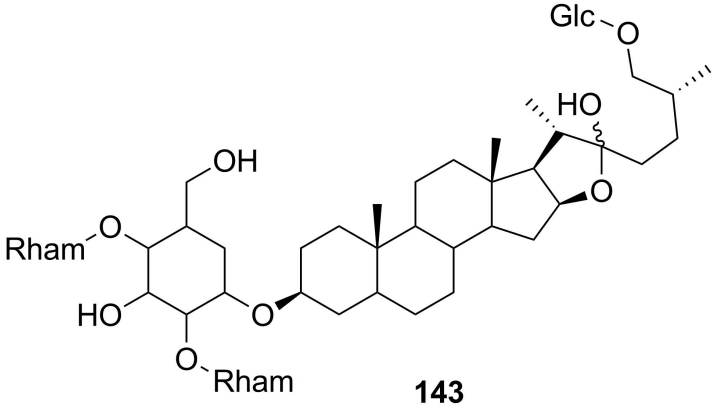

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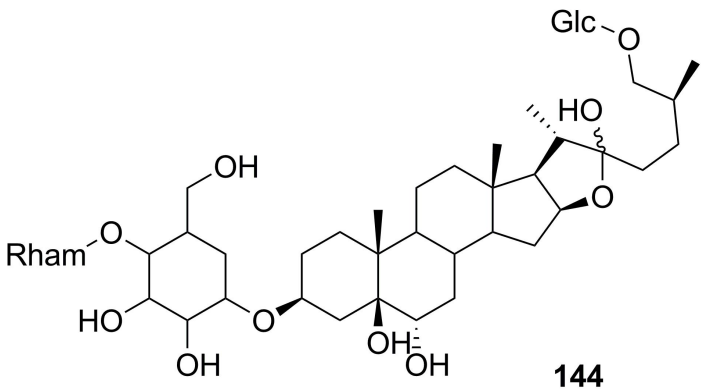

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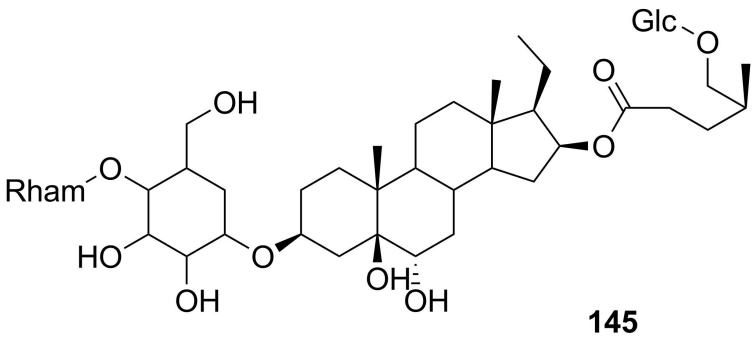
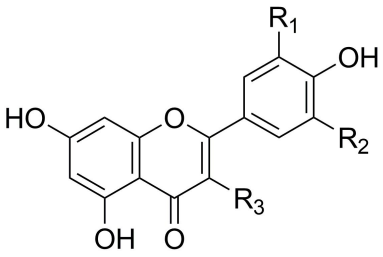
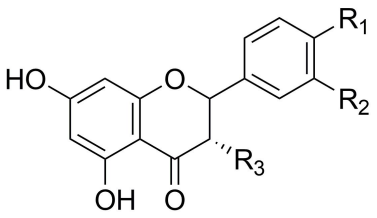


145

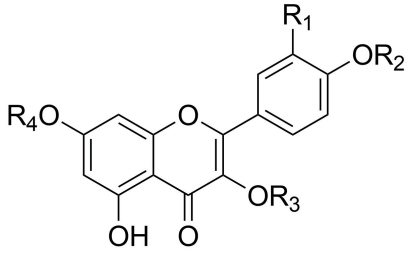
Figure 4

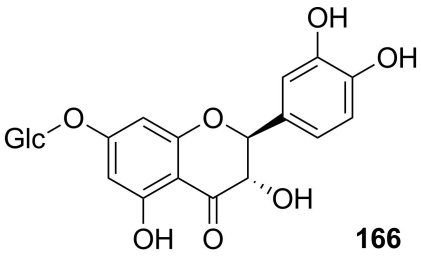


146 R_1=R_2=H, R_3=OH
147 R_2=H, R_1=R_3=OH
148 R_1=R_2=R_3=OH
149 R_1= OH, R_2=R_3=H
150 R_1= OCH_3, R_2=H, R_3= OH



151 R_1=OH, R_2=R_3=H
152 R_1=R_2=R_3=OH





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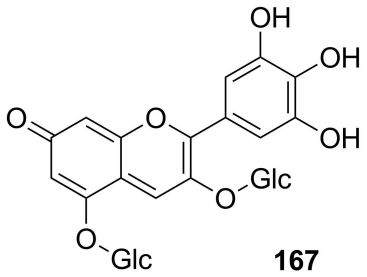
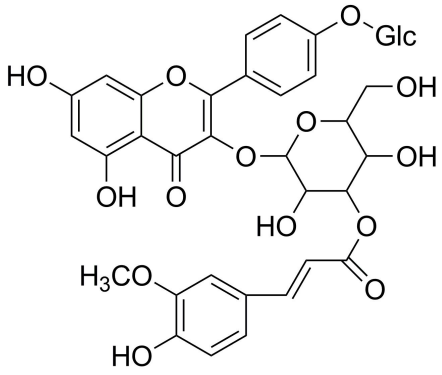


167

153 R_1= OH, R_2=R_4=H, R_3=Glc
154 R_1= OH, R_2=R_4=H, R_3=Rham
155 R_1= OH, R_2=R_4= H, R_3= Glc-Rham
156 R_1=R_2=R_4= H, R_3= Glc-Glc
157 R_1=R_4= H, R_2=R_3= Glc
158 R_1=R_2=R_4= H, R_3= Glc
159 R_1= OCH_3, R_2=R_4= H, R_3= Glc
160 R_1= OCH_3, R_2=R_4= H, R_3= Gal
161 R_1= OH, R_2= Glc, R_3=R_4=H
162 R_1=OH, R_2=R_3= Glc, R_4= H
163 R_1=R_3= H, R_2=R_4= Glc
164 R_1= OCH_3, R_2=R_3= Glc, R_4= H
165 R_1= H, R_2=R_3=R_4= Glc



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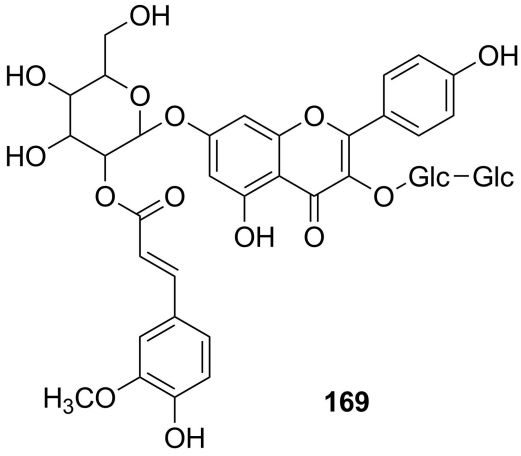

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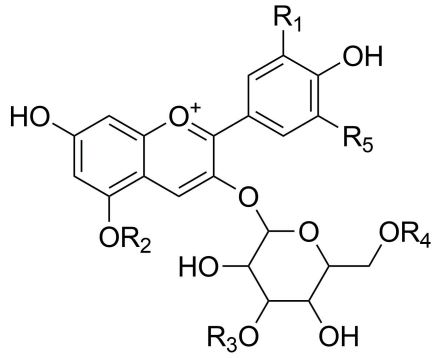
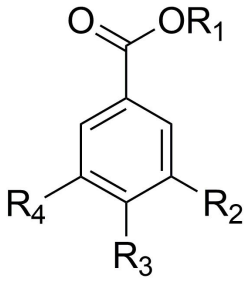
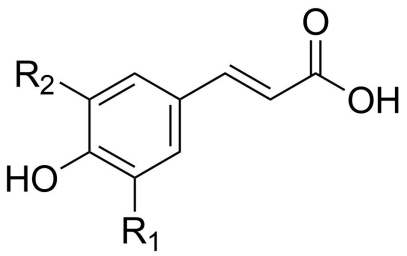


170 R1= OH, R2=R3=R4=R5= H
171 R1= OH, R2=R3=R5= H, R4= CO-CH2-COOH
172 R1= OH, R2=R4=R5= H, R3= CO-CH2-COOH
173 R1= OCH_3, R2=R3=R4=R5= H
174 R1=R5=OCH_3, R2=R3=R4= H

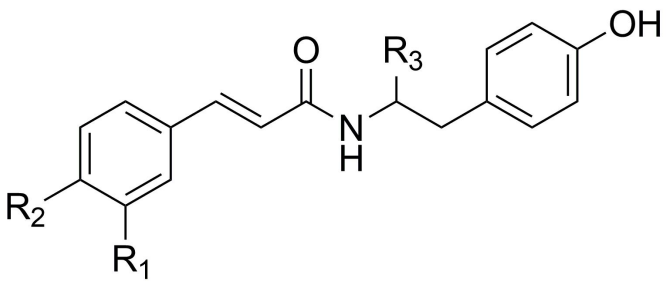
Figure 5



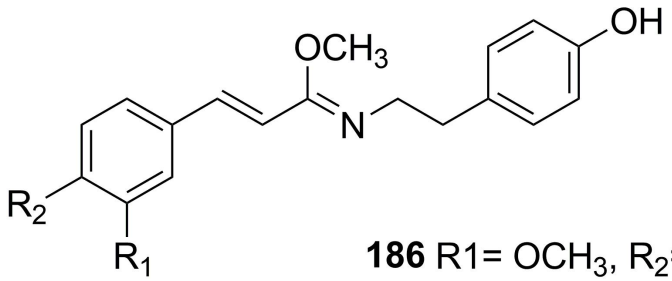
175 R_1=R_4=H, R_2=R_3=OH
176 R_1=R_4=H, R_2=OCH_3, R_3=OH
177 R_1=H, R_2=R_3=R_4=OH



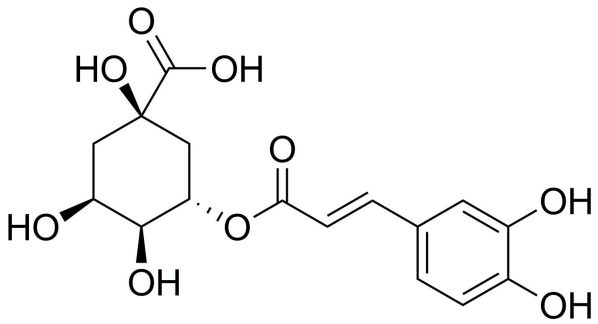
178 R_1=R_2=H
179 R_1=OH, R_2=H
180 R_1=OCH_3, R_2=H
181 R_1=R_2=OCH_3



182 R1= H, R_2= OH, R_3= H
183 R_1= OCH_3, R_2= OH, R_3= H
184 R_1= OH, R_2= OH, R_3= H
185 R_1= H, R_2=OH, R_3= COOH



186 R1= OCH_3, R_2= OCH_3
187 R_1= OH, R_2= OH
188 R_1= OCH_3, R_2= OH



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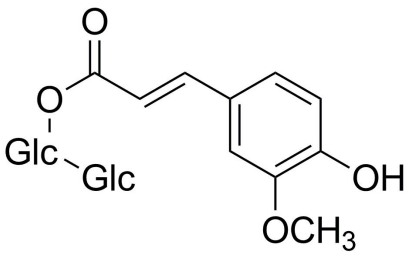

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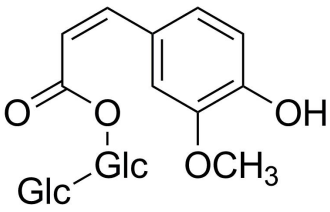

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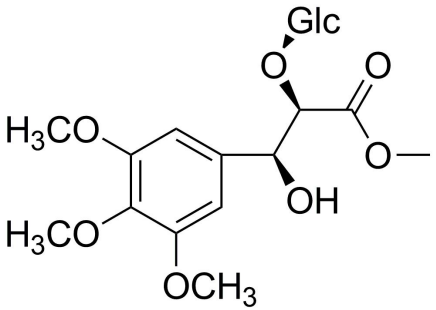

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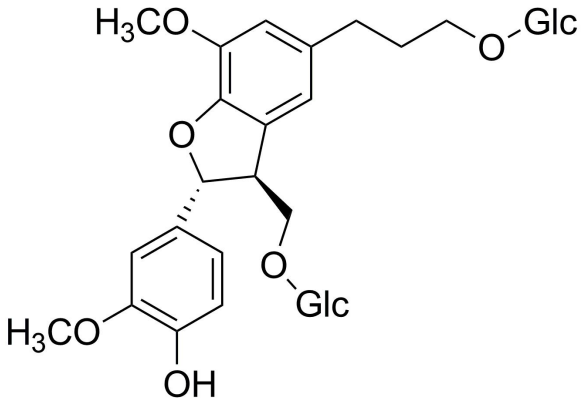

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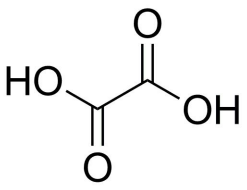
Figure 6



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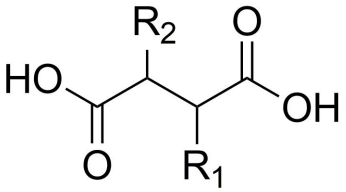
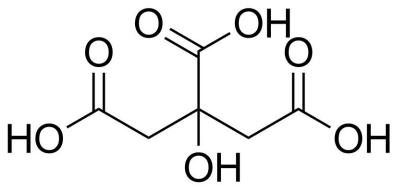


195 R_1= H, R_2= H
196 R_1= OH, R_2= H
197 R_1= OH, R_2= OH



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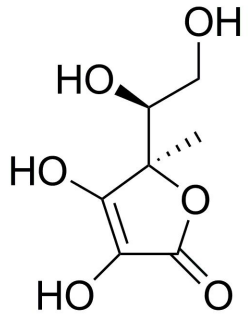

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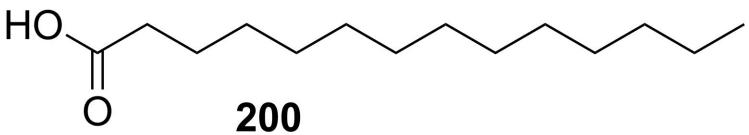

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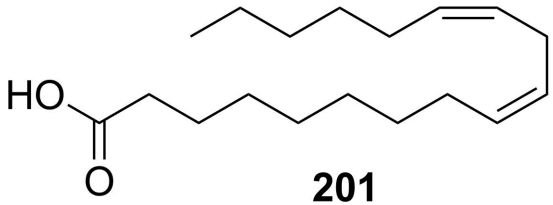

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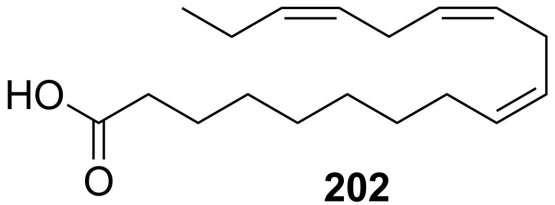

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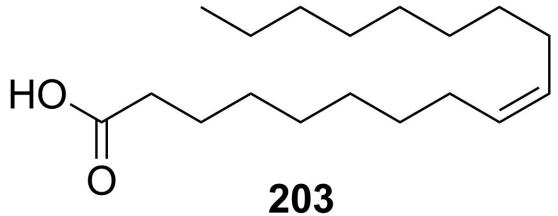

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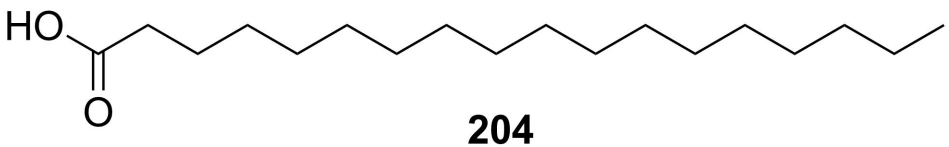

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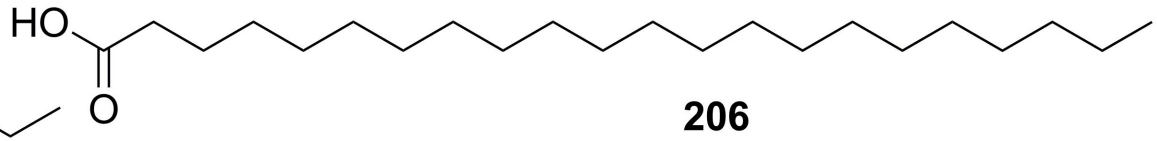

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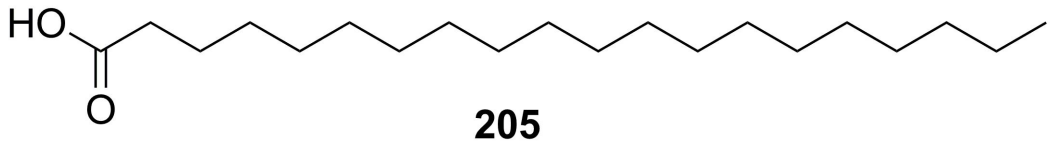

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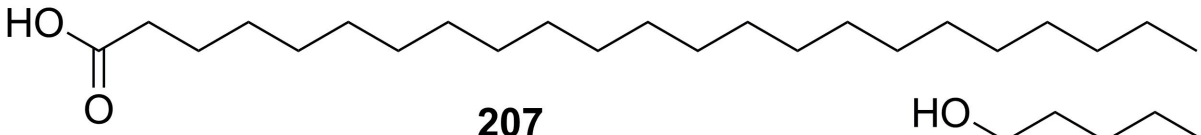

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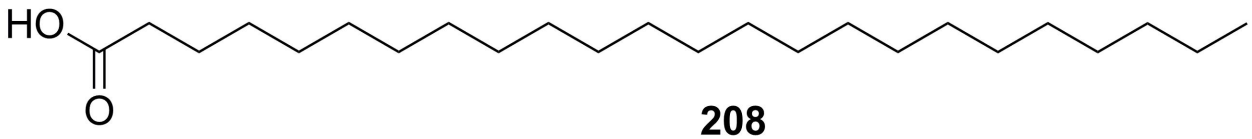

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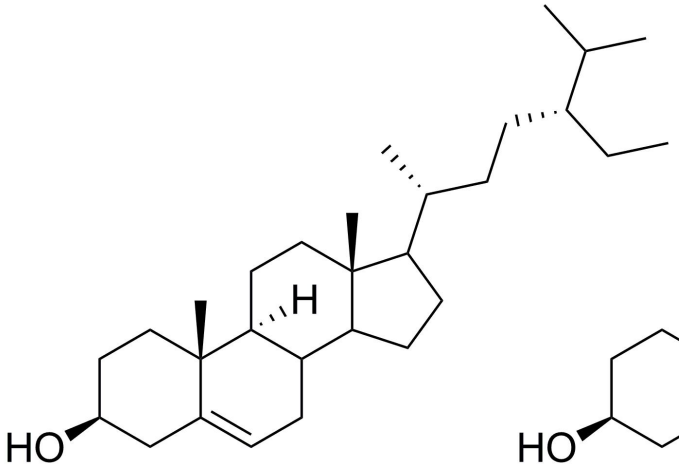

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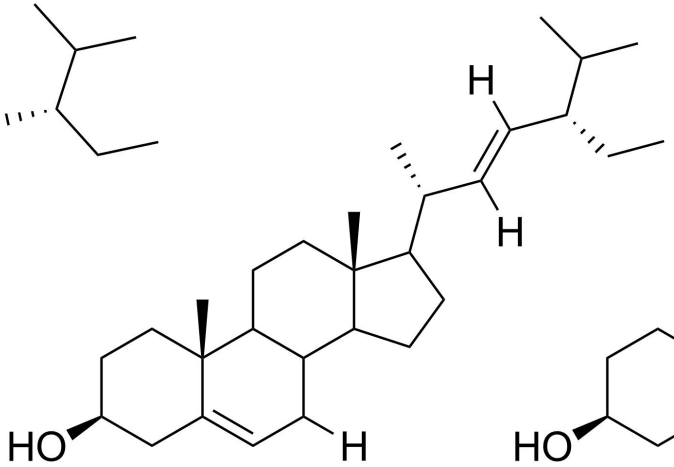

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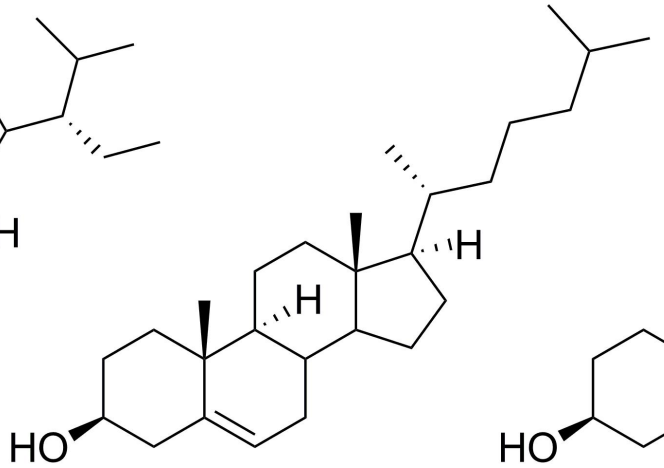

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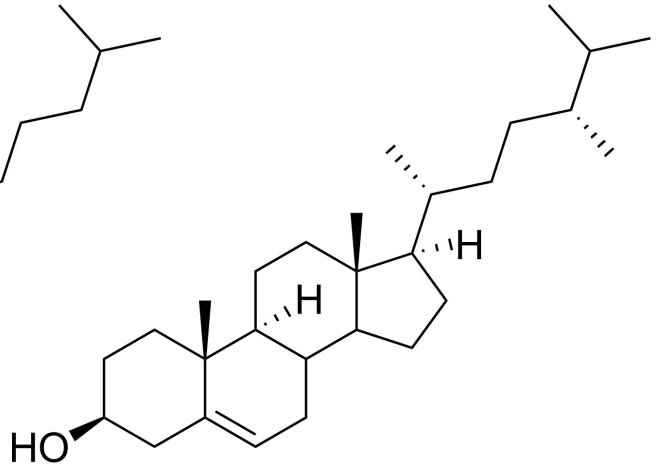

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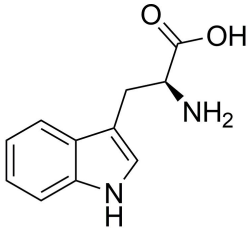

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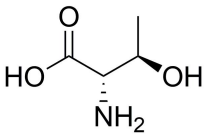

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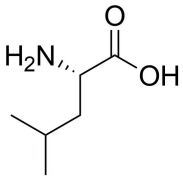

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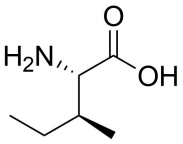

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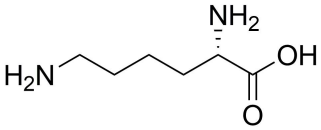

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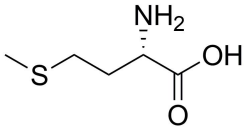

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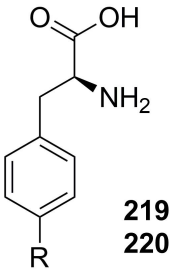
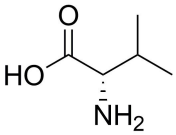


219 R=H
220 R=OH



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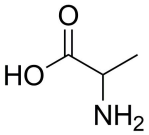

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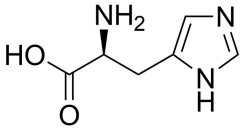

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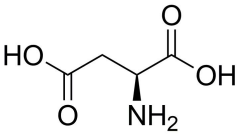

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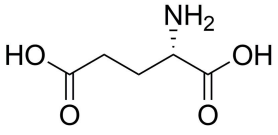

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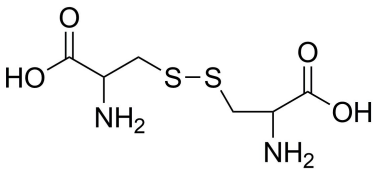

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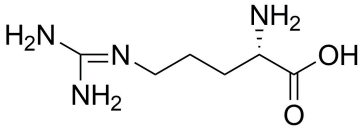

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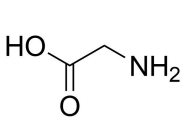

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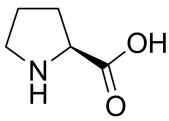

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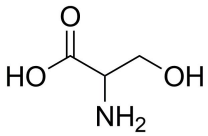

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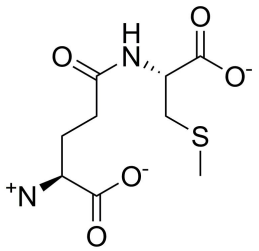

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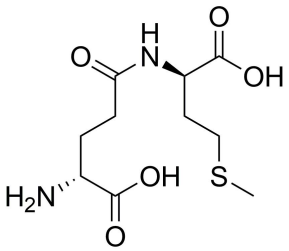

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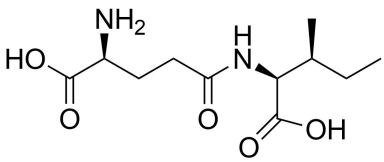

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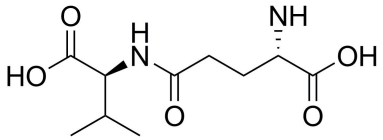

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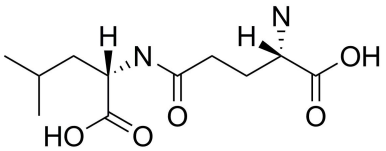

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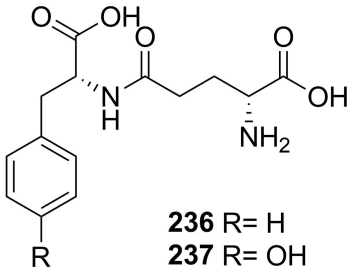
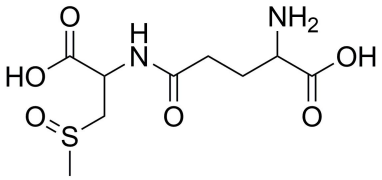


236 R= H
237 R= OH



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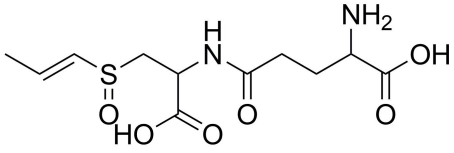

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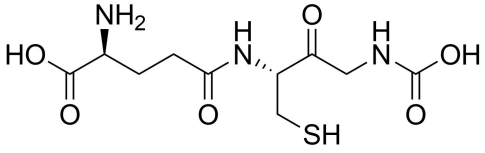

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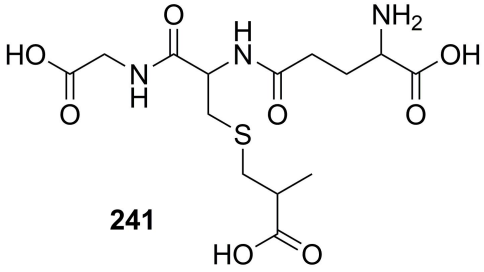

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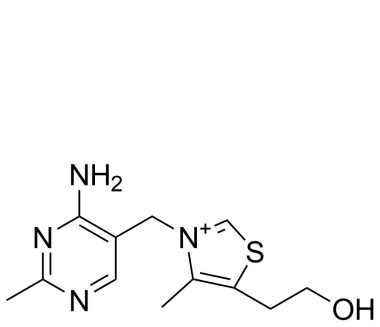

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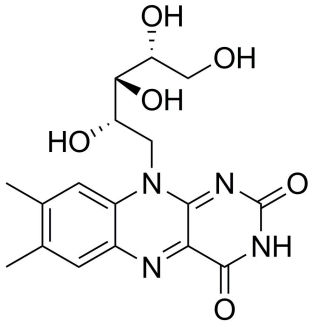

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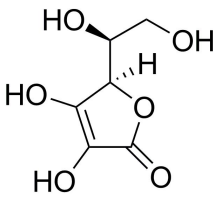

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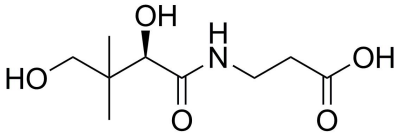

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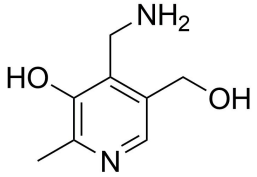

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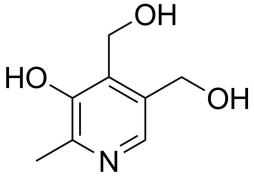

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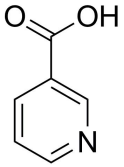

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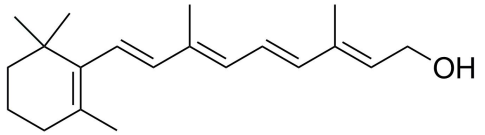

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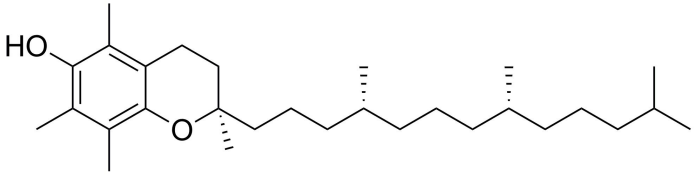

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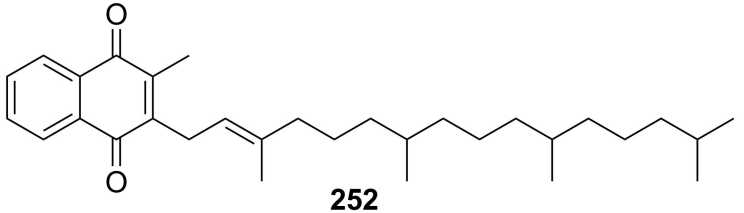

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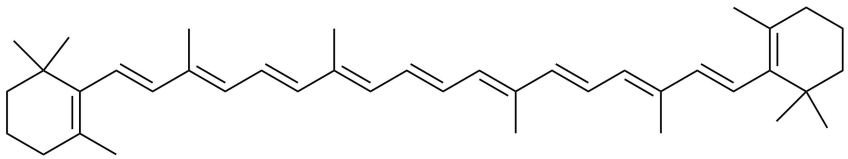

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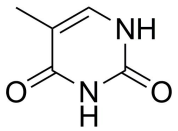

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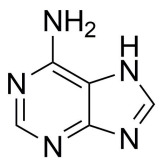

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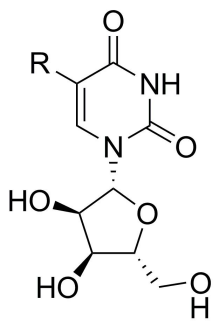
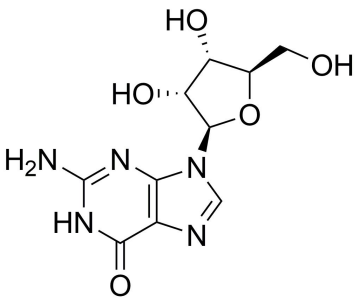


256 R=H
257 R=CH_3



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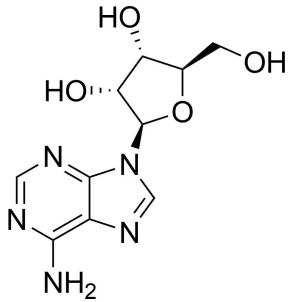

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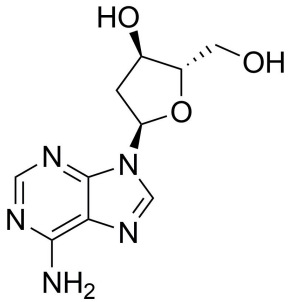


260

Figure 10

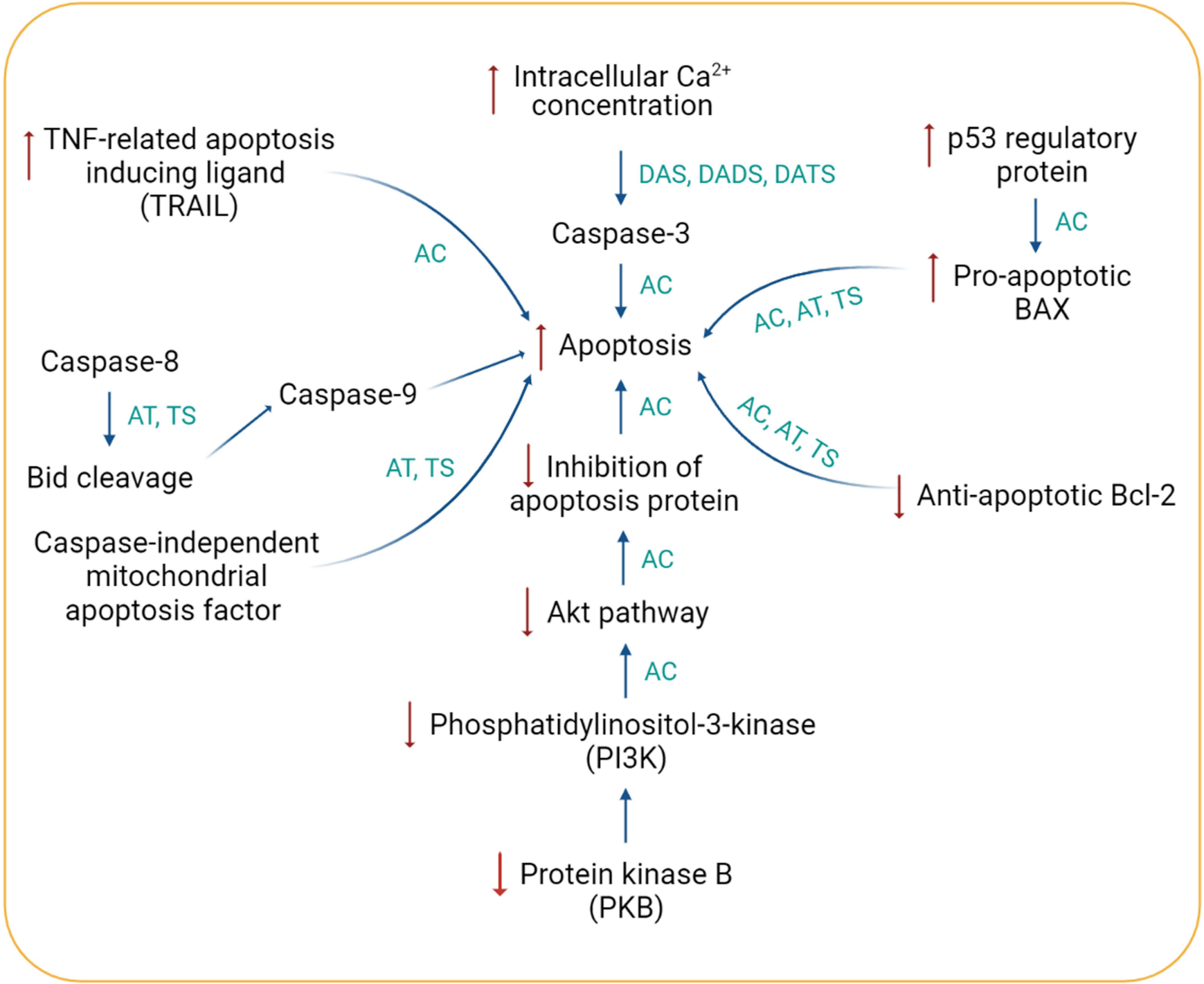
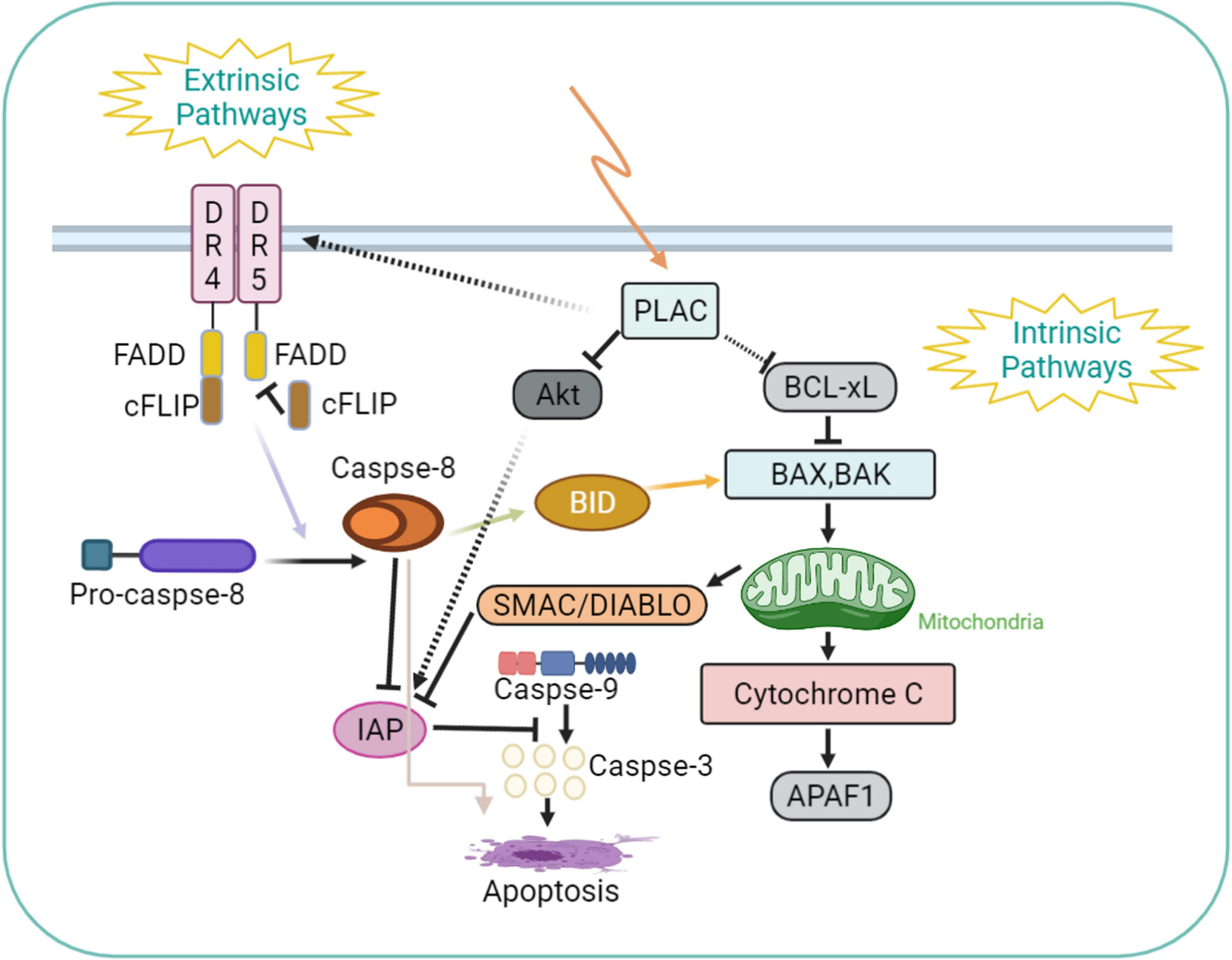

Intracellular Ca^{2+} concentration
TNF-related apoptosis inducing ligand (TRAIL)
DAS, DADS, DATS
p53 regulatory protein
AC
Caspase-3
AC
Pro-apoptotic BAX
AC
AC, AT, TS
Apoptosis
Caspase-8
AT, TS
Caspase-9
AC
AC, AT, TS
Bid cleavage
AT, TS
Inhibition of apoptosis protein
Anti-apoptotic Bcl-2
Caspase-independent mitochondrial apoptosis factor
AC
Akt pathway
AC
Phosphatidylinositol-3-kinase (PI3K)
Protein kinase B (PKB)

Figure 11


Extrinsic Pathways
DR4
DR5
FADD
FADD
cFLIP
cFLIP
Caspse-8
Pro-caspse-8
PLAC
Akt
Intrinsic Pathways
BCL-xL
BAX,BAK
BID
SMAC/DIABLO
Mitochondria
Caspse-9
IAP
Caspse-3
Cytochrome C
APAF1
Apoptosis