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Abstract

Natural remedies have for centuries played a significant role in traditional medicine and continue to be a unique reservoir of new chemical entities in drug discovery and development research. Propolis is a natural substance, collected by bees mainly from plant resins, that has a long history of use as a folk remedy to treat a variety of ailments. The highly variable phytochemical composition of propolis is attributed to differences in plant diversity within the geographic regions from which it is collected. Despite the fact that the last five decades have seen significant advancements in the understanding of the chemistry and biological activity of propolis, a search of the literature has revealed that studies on African propolis to date are rather limited. The aim of this contribution is to report on the current body of knowledge of African propolis, with a particular emphasis on its chemistry and biological activity. As Africa is a continent with a rich flora and a vast diversity of ecosystems, there is a wide range of propolis phytochemicals that may be exploited in the development of new drug scaffolds.

Keywords Africa - Propolis - Biological activity - Chemical diversity - Phytochemicals

Chemical Diversity and Biological Activity of African Propolis

Natalia Blicharska and Veronique Seidel

Contents

1 Introduction

Natural remedies, sourced from plants, microbes, and animal products, have for centuries played a significant role in traditional medicine and continue to represent a unique reservoir of new chemical entities for drug discovery research. Between 1981 and 2014, 50% of all small molecule-approved drugs released on the market were either directly derived from a natural product or synthetic compounds based on a natural product pharmacophore [1].

Propolis, also known as bee glue, is a natural substance produced by honeybees from plant secretions such as resins and sticky exudates on leaf buds and plant wounds (Plate 1). The word propolis is derived from Greek, in which προ (pro) means “at the entrance to” and πόλις (polis) means “community” or “city”. Bees use propolis as a construction and repair material to seal gaps, smooth out internal walls in their hives and as an antiseptic coating to generally protect the hive from external contamination [2–4].

>Plate 1<

The chemical composition of propolis can be highly variable, and this is attributed to differences in plant sources, governed by factors such as climatic conditions and seasons, within the geographical locations from where it is collected [4–6]. Propolis has a long history of use as a natural remedy for a variety of conditions and there has been in recent years a renewed interest in re-investigating the potential of propolis for drug development with some significant advancements in the understanding of its chemistry and biological activity [7–11]. The purpose of this contribution is to report more specifically on the current body of knowledge on the chemistry and biological activity of African propolis.

2 Chemical Diversity of Phytochemicals Isolated from African Propolis

Propolis is a complex mixture composed of resins, wax, fatty acids, essential oils, pollen, sugars, enzymes, minerals, and microelements [11]. Over 500 phytochemicals have been collectively identified in propolis collected from around the world [10]. It is well understood that the phytochemical composition (and subsequent biological activity) of propolis is highly variable and largely depends on the available flora in different locations and season of collection [6].

Indeed, propolis is commonly categorized into distinct chemotypes according to its botanical origin. For example, samples collected from temperate regions tend to possess phytochemicals that are characteristic of poplar bud phenolics due to the main source of propolis in such regions being poplar trees. Thus, “poplar-type” propolis is rich in flavonoids, cinnamic acids and esters, phenolic acids and esters, and other aromatic acids [12]. On the other hand, bees collecting propolis from tropical regions have a wider array of plant sources at their disposal, and propolis from tropical regions is characterised by the presence of other types of phytochemicals such as terpenoids, lignans, stilbenes, benzophenones and phenolic lipids [13–17].

Standard hyphenated techniques (e.g. HPLC-DAD, GC-MS, LC-MS, and LC-MS-MS) have been largely employed to chemically profile propolis samples [18–20]. However, it has to be said that in some cases the true identity of specific phytochemicals could not be conclusively confirmed using the aforementioned techniques alone [21].

For that reason, we decided to focus our literature search for this review solely on phytochemicals from African propolis that have been isolated through the use of various preparative chromatography techniques and characterised unambiguously by means of mass spectrometry and NMR analysis. Our search retrieved a total of 145 phytochemicals from propolis samples originating from nine African countries. The structurallydiverse phytochemicals were grouped into five main chemical classes including some phenylpropanoids, flavonoids, terpenoids, phenolic lipids, and a range of miscellaneous compounds (Figs. 1–8, Tables 1–5) [22–36].

>Figs. 1–8 <

>Tables 1–5<

3 Biological Activity of African Propolis Extracts and Constituents

Extracts of African propolis have been investigated for a range of biological activities including for their antimicrobial, antiparasitic/anti-protozoal, antiviral, anti-oxidant, anti-inflammatory, organ-protective, immunomodulatory, and anticancer properties. Some interesting biological effects have also been reported for specific phytochemicals present in African propolis (Table 6) [37–132].

>Table 6<

3.1 Antimicrobial Activity

3.1.1 **Antibacterial Activity**

The current development of antibiotic-resistance among bacterial pathogens is a global health threat that urgently requires the development of new drugs to fight off infections [133]. Many studies have investigated the antibacterial potential of propolis, but it is important to highlight at this point that the use of inconsistent assay methodologies and extraction techniques, and the screening of chemically non-standardized samples makes it difficult to compare the available data [39, 134, 135].

It has been noted, in agreement with previous observations [136], that extracts of African propolis showed potent activity against Gram-positive bacteria such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pyogenes*, *Streptococcus anginosus*, *Enterococcus faecalis*, *Bacillus subtilis*, *Bacillus cereus*, and beta-hemolytic streptococci [13, 17, 25, 51, 134, 135, 137, 138] and rather weak activity against Gram-negative pathogens like *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Enterobacter cloacae* [13, 17, 25, 32, 39, 51, 134, 135, 137], and non- and alpha-hemolytic streptococci [25].

Interestingly, Egyptian propolis has been found to inhibit the growth of drug-resistant strains of *E. coli* and *S. aureus* [139]. Studies have also reported the ability for African propolis to impair bacterial biofilm formation with Tunisian propolis displaying direct antibiofilm activity on a range of oral pathogens including a range of *Enterococcus*, *Gemella*, and *Streptococcus* spp. [138]. When applied to nanoparticle-treated catheters, Moroccan propolis showed a reduced adherence of methicillin-resistant *Staphylococcus aureus* (MRSA) strains [140].

Few studies have endeavored to identify the phytochemicals responsible for the observed antibacterial effect of African propolis or to unravel the mechanism of action by which these compounds exert their biological effects. However, it has been noted that the presence of flavonoids appears to confer some antibacterial activity to African propolis [25, 26, 141]. In particular, the observation that galangin (present in Algerian and Egyptian propolis) causes damage to bacterial cytoplasmic membranes [54], may explain the observed antibacterial effect of this type of propolis.

3.1.2 **Antifungal Activity**

African propolis has demonstrated variable activity against fungal pathogens including *Aspergillus* spp [142–144], *Candida* spp. [17], *Cryptococcus neoformans* [51], *Colletotrichum*, and *Fusarium* spp. [143].

Studies investigating the antifungal effect of African propolis against *Candida albicans* have afforded mixed results. Good activity against *C. albicans* and *C. neoformans* has been reported for South African propolis [51]. For samples of Egyptian origin, the activity has been reported to be similar to that of ketoconazole and clotrimazole [134]. On the other hand, neither the extracts nor any of the phytochemicals isolated from Kenyan propolis have exhibited activity against *C. albicans* [13].

These results are likely to be explained by the different chemical compositions between South African, Kenyan, and Egyptian propolis. The latter has also been reported to inhibit the growth of *Aspergillus* spp. involved in the production of aflatoxins in foodstuffs [142, 144] and has showed promising antibiofilm activity against *Candida* spp., including drug-resistant strains, which is of particular potential interest in dental care [139, 145].

3.2 Antiparasitic and Antiprotozoal Activity

The global challenge posed by the rise in drug-resistance also applies to diseases caused by parasites, including protozoa [146]. Nigerian and Libyan propolis extracts have demonstrated activity against *Trypanosoma brucei brucei* that was greater than that obtained for individually isolated phytochemicals, suggesting the presence of a synergistic effect between compounds [21, 34, 36]. Libyan propolis has also revealed varying degrees of activity against *Leishmania donovani*, *Plasmodium falciparum*, and *Crithidia fasciculata* [21] and the antitrypanosomal activity of Nigerian propolis has been observed against two multi-drug resistant strains. (3*S*)-vestitol (**54**), 6-prenylnaringenin (**36**), 8-prenylnaringenin (**37**), α-amyrin (**87**) and gerontoxanthone H (**143**) were identified as being responsible for this antiprotozoal effect [29, 34].

Cameroonian and Ghanaian propolis have shown activity against *T. brucei brucei*, with the greatest effect obtained for the deperoxidized derivative of plukenetione C (**131**) [35]. Egyptian propolis has demonstrated activity against *Fasciola gigantica* [141, 147] and *Cryptosporidium* spp. [148] and its combined administration with the antiparasitic drug praziquantel significantly lowered the burden of *Schistosoma mansoni* in infected mice [149].

3.3 Anti-inflammatory Activity

Inflammation is an important physiological response to harmful stimuli, and one that is necessary for tissue repair. Chronic inflammation has been implicated in the pathogenesis of a range of diseases including, neurodegeneration [150], cancer [151], cardiovascular diseases [152], and asthma [153].

The anti-inflammatory effect of Egyptian propolis has been reported in asthmatic mice and attributed to the presence of flavonoids and phenolics [154]. The selective targeting of phosphodiesterase type-4 (PDE4) is a strategy pursued in the search for novel treatments for respiratory diseases associated with inflammation such as asthma [155] and 3β-cycloartenol-26-oic acid (**74**), isolated from Egyptian propolis, has been shown to strongly inhibit the activity of this enzyme. The flavonoids chrysin (**20**) and pinostrobin (**42**) also reduced PDE4 activity [27].

Quercetin (**17**) and galangin (**22**) have been identified as responsible for the anti-inflammatory activity of South African propolis [41]. Caffeic acid phenethyl ester (CAPE) (**7**), present in Algerian propolis, has exerted anti-allergic activity via a reduction in the release of inflammatory mediators such as histamine and leukotrienes [42].

3.4 Anti-oxidant Activity

Oxidative damage to biomolecules, such as DNA, RNA, proteins, enzymes, and lipids, is attributed to an imbalance in the formation and elimination of reactive oxygen (ROS) or nitrogen (RNS) species. This imbalance, and subsequent damage to biomolecules, plays a role in many conditions including cancer [156], neurodegeneration [157], diabetes, and cardiovascular diseases [158, 159]. African propolis possesses varying degrees of anti-oxidant capabilities depending on the presence of varying amounts of anti-oxidant compounds.

It has been observed that propolis extracts rich in polyphenols (e.g. flavonoids and phenolic acids) exhibit the strongest anti-oxidant activity [15, 38, 160–162]. This could be explained through mechanisms such as the direct scavenging of ROS, the chelation of metal ions involved in free radical formation and the inhibition of the activity of enzymes producing ROS [163].

Chrysin (**20**), tectochrysin (**21**), pinostrobin (**42**), 3-β-cycloartenol (**67**), 3*β*-cycloartenol-26-oic acid (**74**), 3*α*-cycloartenol-26-oic acid (**75**) and β-amyrin acetate (**84**), all isolated from Egyptian propolis, have shown radical-scavenging activity as well as xanthine oxidase inhibitory activity [27].

Mangiferonic acid (**71**), methyl-*3β*,27-dihydroxycycloart-24-en-26-oate (**77**), *3β*-hydroxylanostan-9,24-dien-21-oic acid (**93**) and 1'-*O*-

eicosanyl glycerol (**130**), isolated from Cameroonian propolis, showed radical-scavenging activity that was higher than that of their corresponding crude extracts [33].

3.5 Organ-protective Activity

The presence of anti-oxidant compounds, that help counteract cell damage, has often been attributed to the observed protective activity of propolis against a range of organs [164, 165]. When administered prior to the anticancer drug doxorubicin, Algerian propolis has been found to induce cardio-, nephro-, and hepatoprotective effects [166–168].

Egyptian propolis can attenuate the testicular toxicity of the anticancer drug doxorubicin [169]. It has also been reported that it can protect against ovarian toxicity following exposure to the pesticide methoxychlor [170] and limit cytotoxicity (on reproductive organs and the liver) and genotoxicity (chromosomal aberrations in bone marrow cells) induced by the anticancer drug cisplatin [171]. Egyptian propolis also protects against aflatoxin B1-induced hepatotoxicity [172].

Moroccan propolis showed a protective effect against ethylene glycol-induced hepatotoxicity and nephrotoxicity [173]. Tunisian propolis can limit nephrotoxicity following exposure to heavy metals [174] and

Nigerian propolis has hepatoprotective and pancreatoprotective properties [175].

Pinocembrin (**38**), present in Egyptian, Nigerian and Algerian propolis, when administered as a prophylactic long-term treatment to animals with induced cerebral ischemia reperfusion, had neuroprotective activity [76].

3.6 Antiviral and Immunomodulatory Activity

The antiviral effect of African propolis has been poorly investigated. African propolis extracts have only been tested against the Infectious Bursal Disease, the Reovirus, and the Newcastle Disease viruses. Samples showed a reduction in infectivity mean viral titers to varying degrees, with Egyptian propolis exhibiting the highest activity against all viruses [27, 39, 176–178].

Studies investigating the immunomodulatory properties of African propolis are also limited. Egyptian propolis has been shown to strengthen the defense system of the Nile tilapia fish (*Oreochromis niloticus*) [179] and protect rats, through immunostimulation, from the symptomatic manifestations associated with *S. aureus* and *Pasteurella multocida* infections [180–182].

In a study investigating the effect of Egyptian propolis on cutaneous warts, it was demonstrated that treated individuals showed no recurrence of plane and common warts. This was explained partly due to the antiviral and immunomodulatory effects of this type of propolis [183].

3.7 Cytotoxic and Anticancer Activity

Cancer is a major cause of global morbidity and premature mortality and its burden is expected to grow over the coming years [184]. Tunisian propolis has demonstrated potent dose-dependent cytotoxicity against a range of cancer cell lines [138].

Algerian propolis can synergize the antitumor effect of doxorubicin on human pancreatic cancer cells by blocking efflux pump activity, inducing cell cycle arrest and promoting apoptosis [185]. When Algerian propolis was administered to mice with melanoma, a reduction in melanoma tumor growth and increase survival was observed. A prophylactic treatment with Algerian propolis also reduced tumor growth, but with no effect on life prolongation [55, 56].

Egyptian propolis, given alone or in combination with doxorubicin, has shown anti-proliferative and apoptotic effects against PC3 cancer cells that were greater than doxorubicin alone [186]. Mice treated with Egyptian propolis prior to being injected with Ehrlich ascites carcinoma (EAC) cells have been found to live longer than a control group that received no propolis. These findings were attributed to multiple mechanisms of action, including the inhibition of tumor proliferation, induction of apoptosis and immunostimulation. In particular, it has been reported that the administration of propolis, prior to inoculation of EAC cells, arrested the cells in the S-phase and prevented further proliferation. Egyptian propolis has also been also found to induce the sub-G1 apoptosis process in cancerous cells, resulting in tumor reduction [187, 188].

Phenethyl-(*E*)-caffeate (CAPE) (**7**), present in Algerian propolis, significantly increased the antiproliferative and cytotoxic effects of docetaxel and paclitaxel in various prostate cancer cell lines through modulation of the estrogen receptor ER-β [43].

3.8 Other miscellaneous biological effects

The anti-ageing, wound healing, and tissue regenerative properties of African propolis have been investigated for extracts of Algerian propolis revealing potent inhibition of stromelysin-1 (MMP-3), an enzyme involved in the proteolytic degradation of collagen and elastin fibers. Caffeic acid (**1**), chicoric acid (**14**), and chicoric acid methyl ester (**15**), present in

Algerian propolis, were identified as the phytochemicals responsible for this effect. Algerian propolis can also inhibit human plasmin enzymes involved in the pathway leading from pro-MMP-3 to the active MMP-3 enzyme [23].

Moroccan propolis when administered to rats with *Capparis spinosa* honey can trigger a diuretic effect [162] and has the potential to treat and prevent kidney stones, crystaluria, and proteinuria [173]. It has also been reported that Moroccan propolis can inhibit glucosidase and amylase enzymes [189].

Cameroonian propolis has been found to exert estrogenic effects and can help alleviate hot flushes in rats [190]. Nigerian propolis has displayed anti-hyperglycemic and hypocholesterolaemic effects by decreasing blood glucose, glycated hemoglobin (HbA1c), and very low-density lipoprotein (VLDL) levels and elevating high-density lipoprotein (HDL) levels in diabetic rats [191].

4 Conclusion and Perspectives

The use of natural products in the development of new pharmaceuticals has proven to be a well-founded and viable drug discovery strategy so far [1].

The African continent is characterised by a wide range of geographical regions and a rich diversity of ecosystems [192] where a range of different plant species can be used by bees to produce propolis and subsequently exploited by scientists to afford new potential drug templates.

To date, we found that propolis from only nine African countries (of a total of 54) has been investigated for its biological activity and/or phytochemical constituents. The samples investigated have yielded a high diversity of compounds and exhibited a range of biological properties, including antimicrobial, antiparasitic, anti-inflammatory, anti-oxidant, organ-protective, antiviral, immunomodulatory, anticancer, and other miscellaneous effects. In many cases however, little is known about whether the aforementioned effects depend upon the presence of some specific phytochemical(s) or a potentiation between different compounds that may act synergistically.

Much of what is known about the biological activity of African propolis relies on studies testing crude or semi-fractionated extracts that have been poorly chemically-standardized. The lack of quantification (i.e. determination of the nature and relative abundance of phytochemicals in a sample) also prevents the results from different studies to be compared in a meaningful way. Another issue which has limited the progression of scientific knowledge on African propolis is the use of different assay methodologies to screen samples for bioactivity.

This, however, should not discourage further research on this topic because the limited studies to date have already revealed that African propolis has a tremendous potential for providing diverse biologically-active chemicals that can serve as templates for the development of new drugs leads. This includes 7-*O*-dialkylaminoalkyl pectolinarigenines, like **146**, a synthetic derivative of pectolinarigenin (**147**) (Fig. 9) that has strong anti-proliferative activity against human lung carcinoma COR-l23 and A549 cancer cell lines [60], and nymphaeol B (**148**) derivatives which have, so far, showed greater activity against PC-3 prostate cancer cells than 5-fluorouracil [193].

>Fig. 9<

Research on African propolis must be expanded to encompass propolis samples from many different countries and geographical regions in Africa. This will provide a more complete picture of the diversity of propolis phytochemicals available for potential drug design and development. Further research should also aim to standardize screening methods to ensure consistency in methodologies. Altogether, this will allow for the findings of different studies to be more easily compared.

Lastly, research must move beyond the use of extracts in biological assays and focus on isolating phytochemicals and screening them to identify any bioactive compounds. Determining which phytochemicals are biologically-active as well as unraveling their molecular targets will help to determine the mechanisms through which propolis achieves its biological effects. We believe that this review provides a starting point upon which further research investigating, yet unexplored, African propolis samples for the presence of new biologically-active chemical entities may be based.

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Fig. 1 Structures of phenylpropanoids isolated from African propolis

Fig. 2 Structures of flavonoids isolated from African propolis I

Fig. 3 Structures of flavonoids isolated from African propolis II

Fig. 4 Structures of phenolic lipids isolated from African propolis

Fig. 5 Structures of terpenoids isolated from African propolis I

Fig. 6 Structures of terpenoids isolated from African propolis II

Fig. 7 Structures of terpenoids isolated from African propolis III

Fig. 8 Structures of miscellaneous compounds isolated from African propolis

Fig. 9 Compounds **146**–**148**

Plate 1 Propolis sample; photograph: Goldmull, Creative Commons 3.0

Table 1 Phenylpropanoids isolated from African propolis

Compound	Origin	Refs.
Caffeic acid (**1**)	Algeria	[22, 23]
Prenyl caffeate (**2**)	Algeria	[22]
Methyl caffeate (**3**)	Algeria	[22]
Isopentyl caffeate (**4**)	Algeria	[22]
2-Methyl-2-butenyl (*E*)-caffeate (**5**)	Algeria	[15]
3-Methyl-3-butenyl-(*E*)-caffeate (**6**)	Algeria	[15]
Phenethyl-(*E*)-caffeate (CAPE) (**7**)	Algeria	[15]
p-Coumaric acid (**8**)	Algeria	[22]
p-Coumaric acid methyl ester (**9**)	Algeria	[22]
Cinnamic acid (**10**)	Algeria	[22]
Isoferulic acid (**11**)	Algeria Egypt	[22] [24]
Caftaric acid (**12**)	Algeria	[23]
Caftaric acid methyl ester (**13**)	Algeria	[23]
(+)-Chicoric acid (**14**)	Algeria	[23]
(+)-Chicoric acid methyl ester (**15**)	Algeria	[23]

Table 2 Flavonoids isolated from African propolis

Compound	Origin	Refs.
Acacetin (**16**)	Algeria	[22]
Quercetin (**17**)	Algeria	[22]
3-*O*-Methyl-quercetin (**18**)	Algeria	[22]
Kaempferol (**19**)	Algeria	[15, 22]
Chrysin (**20**)	Algeria Egypt	[15, 22, 25, 26] [24, 27]
Tectochrysin (**21**)	Algeria Egypt	[22] [24, 27]
Galangin (**22**)	Algeria Egypt	[15, 22] [24]
Galangin-5-*O*-methyl ether (**23**)	Egypt	[24]
Myricetin-3,7,4’,5’-tetramethyl ether (**24**)	Algeria Tunisia	[15] [28]
Apigenin (**25**)	Algeria	[15, 25, 26]
Pectolinarigenin (**26**)	Algeria	[25, 26]
Pilosin (**27**)	Algeria	[25, 26]
Ladanein (**28**)	Algeria	[25, 26]
Macarangin (**29**)	Kenya Nigeria	[13] [29]
Izalpinin (**30**)	Egypt	[24]
Pachypodol (**31**)	Tunisia	[28]
3,3’-Dimethoxy-5,7,4’-trihydroxyflavone (**32**)	Egypt	[24]
3-Methoxy-5,7,4’-trihydroxyflavone (**33**)	Egypt	[24]
Quercetin-3,7-di-*O*-methyl ether (**34**)	Egypt	[24]
Naringenin (**35**)	Algeria	[22]
6-Prenylnaringenin (**36**)	Nigeria	[29]
8-Prenylnaringenin (**37**)	Nigeria	[29]
Pinocembrin (**38**)	Algeria Nigeria Egypt	[22] [29] [24]
Pinobanksin (**39**)	Algeria	[15]
Pinobanksin-3-acetate (**40**)	Algeria	[15,22]
Pinobanksin-3-(*E*)-caffeate (**41**)	Algeria	[15]
Pinostrobin (**42**)	Algeria Egypt	[22] [24,27]
Isonymphaeol C (**43**)	Egypt	[30]
Isonymphaeol B (**44**)	Egypt	[31]

Isonymphaeol D (**45**)	Egypt	[31]
Nymphaeol B (**46**)	Egypt Nigeria	[31] [29]
Lonchocarpol A (**47**)	Cameroon Congo	[17] [17]
6,8-Diprenylaromadendrin (**48**)	Cameroon	[17]
Lespedezaflavanone C (**49**)	Cameroon	[17]
6,8-Diprenyleriodictyol (**50**)	Congo	[17]
Liquiritigenin (**51**)	Nigeria	[29]
Genistein (**52**)	Algeria	[22]
Calycosin (**53**)	Nigeria	[29]
(3*S*)-Vestitol (**54**)	Nigeria	[29]

Table 3 Terpenoids isolated from African propolis

Compound	Origin	Refs.
α-Terpineol (**55**)	Cameroon	[17]
18-Hydroxy-*cis*-clerodan-3-ene-15-oic acid (**56**)	Algeria	[15]
Cistadiol (**57**)	Algeria	[15]
Isoagathotal (**58**)	Algeria	[15]
Imbricatoloic acid (**59**)	Algeria	[15]
Cupressic Acid (**60**)	Algeria	[15]
Isocupressic acid (**61**)	Algeria	[15]
Torulosol (**62**)	Algeria	[15]
Agathadiol (**63**)	Algeria	[15]
Torulosal (**64**)	Algeria	[15]
Totarol (**65**)	Algeria	[22]
Pimaric acid (**66**)	Algeria	[22]
3*β*-Cycloartenol (**67**)	Cameroon Egypt	[16] [27]
Cycloart-12,25-dien-3*β*-ol (**68**)	Cameroon	[32, 33]
Ambonic acid (**69**)	Cameroon Nigeria	[16] [34]
Ambolic acid (**70**)	Cameroon	[16, 33]
Mangiferonic acid (**71**)	Cameroon Nigeria	[16, 33] [34]
27-Hydroxymangiferonic acid (**72**)	Cameroon	[33]
Mangiferolic acid (**73**)	Cameroon	[16]
3*β*-Cycloartenol-26-oic acid (**74**)	Egypt	[27]
3*α*-Cycloartenol-26-oic acid (**75**)	Egypt	[27]
Isomangiferolic acid (**76**)	Cameroon	[16]
Methyl-3*β*,27-dihydroxycycloart-24-en-26-oate (**77**)	Cameroon	[33]
Betulinaldehyde (**78**)	Cameroon	[17]
Betulin (**79**)	Cameroon	[33]
Lupenone (**80**)	Cameroon Congo	[17, 32] [17]
Lupeol (**81**)	Cameroon	[16, 32]
Lupeol acetate (**82**)	Cameroon	[17, 32]
β-Amyrin (**83**)	Cameroon	[16, 17]
β-Amyrin acetate (**84**)	Egypt Cameroon	[27] [17]
3α-Hydroxy-olean-12-en-30-ol (**85**)	Cameroon	[17]
Erythrodiol (**86**)	Cameroon	[17, 32]
α-Amyrin (**87**)	Cameroon Nigeria	[16,17] [34]

α-Amyrone (**88**)	Cameroon	[17]
25-Cyclopropyl-3*β*-hydroxyurs-12-ene (**89**)	Cameroon	[32]
Pseudotaraxasterol acetate (**90**)	Cameroon	[17]
Taraxasterol acetate (**91**)	Cameroon	[17]
Lanosterol (**92**)	Cameroon	[17]
3*β*-Hydroxylanostan-9,24-dien-21-oic acid (**93**)	Cameroon	[33]
β-Sitosterol (**94**)	Cameroon	[33]
Bacchara-12,21-dien-3*β*-ol (**95**)	Cameroon	[17]

Table 4 Phenolic lipids isolated from African propolis

Compound	Origin	Refs.
3-Undecyl phenol (**96**)	Cameroon	[16]
3-Tetradecylphenol (**97**)	Cameroon	[16]
3-Pentadecylphenol (**98**)	Cameroon	[16]
3-Hexadecylphenol (**99**)	Cameroon	[16]
3-Heptadecylphenol (**100**)	Cameroon	[16]
3-Nonadecylphenol (**101**)	Cameroon	[16]
3-((10’*Z*)-Pentadecenyl)-phenol (**102**)	Cameroon	[16]
3-((12’*Z*)-Pentadecenyl)-phenol (**103**)	Cameroon	[16]
3-((8’*Z*)-Heptadecenyl)-phenol (**104**)	Cameroon	[16]
3-((12’*Z*)-Heptadecenyl)-phenol (**105**)	Cameroon	[16]
3-((14’*Z*)-Heptadecenyl)-phenol (**106**)	Cameroon	[16]
3-((13’Z)-Nonadecenyl)-phenol (**107**)	Cameroon	[16]
3-((14’*Z*)-Nonadecenyl)-phenol (**108**)	Cameroon	[16]
5-Pentadecylresorcinol (**109**)	Cameroon	[16]
5-Hexadecylresorcinol (**110**)	Cameroon	[16]
5-Heptadecylresorcinol (**111**)	Cameroon	[16]
5-((10’*Z*)-Pentadecenyl)-resorcinol (**112**)	Cameroon	[16]
5-((8’*Z*)-Heptadecenyl)-resorcinol (**113**)	Cameroon	[16]
5-((11’Z)-Heptadecenyl)-resorcinol (**114**)	Cameroon	[16]
5-((12’*Z*)-Heptadecenyl)-resorcinol (**115**)	Cameroon	[16]
5-((14’*Z*)-Hheptadecenyl)-resorcinol (**116**)	Cameroon	[16]
5-((14’*Z*)-Nonadecenyl)-resorcinol (**117**)	Cameroon	[16]

Table 5 Miscellaneous compounds isolated from African propolis

Compound	Origin	Refs.
Tyrosol (**129**)	Algeria	[22]
1'-*O*-Eicosanyl glycerol (**130**)	Cameroon	[33]
Deperoxidised derivative of plukenetione C (**131**)	Cameroon	[35]
Medicarpin (**132**)	Nigeria	[29]
(+)-Sesamin (**133**)	Libya	[36]
Riverinol (**134**)	Nigeria	[29]
Tetrahydrojusticidin B (**135**)	Kenya	[13]
6-Methoxydiphyllin (**136**)	Kenya	[13]
Phyllamyricin C (**137**)	Kenya	[13]
(*E*)-Resveratrol (**138**)	Algeria	[22]
5-((*E*)-3,5-Dihydroxystyryl)-3-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)benzene-1,2-diol (**139**)	Ghana	[35]
(*E*)-5-(2-(8-Hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)-2*H*-chromen-6-yl)vinyl)-2-(3-methylbut-2-en-1-yl) benzene-1,3-diol (**140**)	Ghana	[35]
Schweinfurthin A (**141**)	Kenya	[13]
Schweinfurthin B (**142**)	Kenya	[13]
Gerontoxanthone H (**143**)	Nigeria	[34]
6-Deoxy-γ-mangostin (**144**)	Nigeria	[34]
1,7-Dihydroxy-3-*O*-(3-methylbut-2-enyl)-8-(3-methylbut-2-enyl) xanthone (**145**)	Nigeria	[34]

Table 6 Biological studies performed on phytochemicals from African propolis

Compound	Tested Biological Activity	Refs.
Caffeic acid (**1**)	Antimicrobial Anti-oxidant Antifibrinolytic, anticollagenolytic	[37] [13, 38–40] [23]
Phenethyl-(*E*)-caffeate (CAPE) (**7**)	Antimicrobial Anti-oxidant Anti-inflammatory Anticancer	[41] [13, 38] [42] [43]
p-coumaric acid (**8**)	Antimicrobial	[44]
Caftaric acid (**12**)	Antifibrinolytic	[23]
Caftaric acid methyl ester (**13**)	Antifibrinolytic	[23]
(+)-Chicoric acid (**14**)	Antifibrinolytic, anticollagenolytic	[23]
(+)-Chicoric acid methyl ester (**15**)	Antifibrinolytic, anticollagenolytic	[23]
Acacetin (**16**)	Anticancer	[45–47]
	Aromatase inhibition	[48]
Quercetin (**17**)	Antimicrobial Anti-oxidant Anti-inflammatory Anticancer Myeloperoxidase inhibition	[41] [22, 38, 49] [41] [50] [22]
Kaempferol (**19**)	Anti-oxidant	[38]
Chrysin (**20**)	Antimicrobial Anti-oxidant Anti-inflammatory Anticancer	[51, 52] [27] [27] [27]
Tectochrysin (**21**)	Anti-oxidant Anti-inflammatory	[27] [53]
Galangin (**22**)	Antimicrobial Anti-inflammatory Anticancer	[51, 54] [41] [55, 56]
Myricetin-3,7,4’,5’-tetramethyl ether (**24**)	Anticancer	[57]
Apigenin (**25**)	Estrogenic	[58]
Pectolinarigenin (**26**)	Anti-inflammatory	[59]

	Anticancer Hepatoprotective	[60, 61] [62]
Ladanein (**28**)	Anticancer Antiviral	[63] [64]
Macarangin (**29**)	Antimicrobial Antiprotozoal Anti-oxidant	[13] [29] [13]
Izalpinin (**30**)	Anti-oxidant Anti-inflammatory Antimuscarinic	[65, 66] [53] [66]
Pachypodol (**31**)	Antiviral Anticancer	[67] [50, 68, 69]
6-Prenylnaringenin (**36**)	Tyrosinase inhibition Anticancer Antiprotozoal	[70] [71, 72] [29]
8-Prenylnaringenin (**37**)	Antimicrobial Antiprotozoal Anti-oxidant Anticancer Estrogenic	[73] [29] [74] [71, 72] [75]
Pinocembrin (**38**)	Antimicrobial Anti-oxidant Neuroprotective Anti-inflammatory Anti-apoptotic Aromatase inhibition, estrogenic Antiprotozoal	[37, 51, 52] [27] [76] [76] [76] [48] [29]
Pinobanksin (**39**)	Antimicrobial	[37, 52]
Pinobanksin-3-acetate (**40**)	Antimicrobial	[51]
Pinostrobin (**42**)	Antimicrobial	[52]
	Phosphodiesterase and acetylcholinesterase inhibition Anti-oxidant Anticancer	[27] [27] [77]
Isonymphaeol C (**43**)	Antimicrobial	[30]
Isonymphaeol B (**44**)	Anti-oxidant Anticancer	[78, 79] [80]
Isonymphaeol D (**45**)	Antimicrobial	[31]
Nymphaeol B (**46**)	Antimicrobial Antiprotozoal Anti-oxidant	[40, 81] [29, 82] [40, 78]

	Anticancer	[80, 82]
Lonchocarpol A (**47**)	Antimicrobial Antiprotozoal Anti-oxidant Anti-inflammatory Anticancer	[83] [84] [74] [85] [74]
Liquiritigenin (**51**)	Anti-inflammatory Xanthine oxidase inhibition Estrogenic	[86] [87] [88]
Genistein (**52**)	Estrogenic	[58]
Calycosin (**53**)	Antiprotozoal	[29]
(3*S*)-Vestitol (**54**)	Antiprotozoal	[29, 89]
Cistadiol (**57**)	Antiprotozoal	[90]
Isoagathotal (**58**)	Antimicrobial Anticancer	[52] [77]
Cupressic Acid (**60**)	Antimicrobial, anti-oxidant Hepatoprotective	[91] [91]
Isocupressic acid (**61**)	Antimicrobial Anti-oxidant Anticancer Hepatoprotective	[52, 91] [91] [77, 92] [91]
Agathadiol (**63**)	Antimicrobial Anticancer	[52] [77]
Torulosal (**64**)	Antimicrobial	[93]
Totarol (**65**)	Antimicrobial	[52]
Pimaric acid (**66**)	Retinoic acid receptor activation Anti-atherosclerotic	[94] [95]
3β-Cycloartenol (**67**)	Anti-oxidant Acetylcholinesterase inhibition	[27] [27]
Cycloart-12,25-dien-3β-ol (**68**)	Antimicrobial	[32]
Ambonic acid (**69**)	Antiprotozoal	[34]
Mangiferonic acid (**71**)	Antiprotozoal	[34]
	Antimicrobial	[96]
	Anti-oxidant	[33, 96]
	Anticancer	[96, 97]
Mangiferolic acid (**73**)	Anticancer	[97]
3β-Cycloartenol-26-oic acid (**74**)	Anti-oxidant Acetylcholinesterase inhibition	[27] [27]

	Phosphodiesterase inhibition	[27]
3*α*-Cycloartenol-26-oic acid (**75**)	Anti-oxidant Acetylcholinesterase inhibition	[27] [27]
Isomangiferolic acid (**76**)	Anticancer	[97]
Methyl-3*β*,27-dihydroxycycloart-24-en-26-oate (**77**)	Anti-oxidant	[33]
Betulin (**79**)	Anticancer Immunomodulatory Anti-inflammatory Antiprotozoal Antimicrobial Antiviral	[98] [99] [100] [100] [100] [100]
Lupenone (**80**)	Anti-inflammatory Anti-oxidant Anticancer	[101] [96] [96]
Lupeol (**81**)	Antiporotozoal Antimicrobial, anti-oxidant Anticancer	[89] [96] [98]
β-Aamyrin (**83**)	Antiprotozoal	[89]
β-Amyrin acetate (**84**)	Anti-oxidant	[27]
Erythrodiol (**86**)	Antimicrobial Anti-oxidant Anticancer Antiplatelet	[32, 44] [102] [102, 103] [104]
α-Amyrin (**87**)	Anti-inflammatory Antiprotozoal	[101] [34]
25-Cyclopropyl-3*β*-hydroxyurs-12-ene (**89**)	Antimicrobial	[32]
3*β*-Hydroxylanostan-9,24-dien-21-oic acid (**93**)	Anti-oxidant	[33]
β-Sitosterol (**94**)	Anti-inflammatory Analgesic, antiparasitic, antimutagenic Anticancer Antihyperglycemic Immunomodulatory Antifertility Anti-oxidant	[105] [106] [107] [108] [109] [110] [111]

	Antimicrobial	[112]
3-((10’*Z*)-Pentadecenyl)-phenol (**102**)	Acetylcholinesterase inhibition	[113]
5-Pentadecylresorcinol (**109**)	Anti-inflammatory Anticancer DNA-cleaving activity	[114] [115–117] [118]
5-Heptadecylresorcinol (**111**)	Antiviral Anti-inflammatory Anticancer	[119] [114] [120]
5-((10’*Z*))-Pentadecenyl)-resorcinol (**112**)	Cytochrome P450s, P-glycoprotein and pregnane X receptor inhibition	[121]
5-((8’*Z*)-Heptadecenyl)-resorcinol (**113**)	Antimicrobial DNA-cleaving activity	[122] [118]
5-((11’*Z*)-Heptadecenyl)-resorcinol (**114**)	Anti-inflammatory	[114]
5-((12’*Z*)-Heptadecenyl)-resorcinol (**115**)	Anticancer	[123]
5-((14’*Z*)-Nonadecenyl)-resorcinol (**116**)	Antiviral Anticancer	[119] [120]
1'-*O*-Eicosanyl glycerol (**130**)	Anti-oxidant	[33]
Deperoxidised derivative of plukenetione C (**131**)	Antiprotozoal	[35]
Medicarpin (**132**)	Antiprotozoal	[29, 89]
(+)-Sesamin (**133**)	Antiprotozoal Anti-inflammatory	[36] [124, 125]
Riverinol (**134**)	Antiprotozoal	[29]
6-Methoxydiphyllin (**136)**	Antimicrobial	[13]
Phyllamyricin C (**137**)	Antimicrobial Anti-inflammatory	[13] [126]
(*E*)-Resveratrol (**138**)	Cancer chemopreventive Anti-inflammatory Cardioprotective Anti-obesity	[127] [128] [129] [130]
5-((*E*)-3,5-Dihydroxystyryl)-3-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)benzene-1,2-diol (**139**)	Antiprotozoal	[35]
(*E*)-5-(2-(8-Hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)-2*H*-chromen-6-yl) vinyl)-2-(3-methylbut-2-en-1-yl)benzene-1,3-	Antiprotozoal	[35]

diol (**140**)		
Schweinfurthin A **(141**)	Antimicrobial	[13]
	Anticancer	[131, 132]
Schweinfurthin B (**142**)	Antimicrobial	[13]
	Anticancer	[131]
Gerontoxanthone H (**143**)	Antiprotozoal	[34]
6-Ddeoxy-γ-mangostin (**144**)	Antiprotozoal	[34]
1,7-Dihydroxy-3-*O*-(3-methylbut-2-enyl)-8-(3-methylbut-2-enyl)xanthone (**145**)	Antiprotozoal	[34]