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Review Article

BEE PROPOLIS (*BEE*'S GLUE): A PHYTOCHEMISTRY REVIEW

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ABSTRACT

Propolis, also called '*Bee* glue', is resinous material collected by *Bee*s from flowers, buds, and exudates of plants. Literature survey were conducted using different electronic databases, like PubMed, Scifinder, and Indian scientific database. The phytoconstituents composition in the *Bee Propolis* varies and depends upon the flora in the location; more than 500 compounds have been isolated and identified till now. They belong to such assorted chemical classes as polyphenols like, phenylpropanoids, chalcone, terpenenes, lignans, coumarins, aromatic acids and their esters. This current review is an attempt to compile data, which will give information of constituents present in *Propolis*.

Keywords: *Propolis*, Pinobanksin 3-acetate, Phytochemistry, Mummifying corpses

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INTRODUCTION

The term ''*Propolis*'' emanates from the Greek word coined by Aristotle, pro (before) and polis (city), meaning, Before the City, or Defender of the City [1]. *Bee Propolis* (*Bee*'s glue) is a resinous, gummy and balsamic material collected from flora by honey Bees (*Apis mellifera* L. belongs to Apidae family, genus Apis) used as construction and insulating material their hive. It is not only used as a construction material but also to protect the hive from microbial growth (fungi and bacteria) [2]. The composition of *Bee Propolis* varies on its botanical original and it has been reported that *Bee Propolis* helps to maintain homeostasis, reduce vibration, keep air flow in check, prevent hive against squatter and prevent putrefaction [3].

Description

Most of the *Bee Propolis* are opaque shiny irregular in shape and is solid at room temperature and become sticky above room temperature. It is dark green or brown in color having a sweet taste but can be bitter too. The composition, aroma and color of the *Bee Propolis* vary from hive to hive, season to season, Bee species, botanical source and geographical conditions prevailing at the location from where the resin is collected by honey Bees [4].

Traditional uses

Propolis has been known from at least 300 BC for its medicinal values in the world. For the Egyptians, the *Bee* was holy and they used *Propolis* to the art of mummifying corpses and as an antibiotic [5]. The Romans, seeing the Bee as God Jupiter convert the lady Mellisa into a Bee and use to cure some lesions of the skin. *Propolis* has been anciently known to Greeks for healing qualities. It also was used in the Boer war for tissue regeneration and wound healing [6]. In the Balkan States it's still used for the treatment of wounds and burns, sore throat, stomach ulcer [7] Traditionally ethanol extract of *Propolis*, has been known for anti-inflammatory effect for centuries [8]. *Bee Propolis* has been used pragmatic for centuries as an immunomodulatory agent [9]. It has been reported that from 12th century *Bee Propolis* was using as remedies in the mouth, throat infections, and dental caries [10].

Phytochemistry

Bee Propolis is official in the United States Pharmacopeia and natural health product monograph Canada [11, 12]. Now days engross has been ascending about its phytochemistry and pharmacological property. The phytoconstituents composition in the *bee propolis* varies and depends upon the flora in the location; more than 500 compounds have been isolated and identified till now. The main phytoconstituents reported to have been isolated and identified from the *Bee Propolis* are polyphenolics, Chalcone, triterpenes, aromatic acids and their esters [13-17].

The chemical analysis of red-type Cuban *Propolis* revealed the presence of 11 isoflavonoids long with gallic acid, isoliquiritigenin, and (-)-liquiritigenin [18]. It has been reported that the main phytoconstituents in the *Bee Propolis* are flavonoids and their aglycones moiety [19, 20]. The main phenolics compounds flavonoids with an unsubstituted ring are pinobanksin, pinocembrin-7-methyl ether, pinobanksin 3-acetate, pinocembrin, chrysin, galangin, tectochrysin, apigenin, kaempferol and quercetin and the flavones components are eupatorin, hispidulin, 5-hydroxy-6,7,3′,4′-tetra methoxy flavone are also present [21-23].

The other phenolics compounds isolated are 3-prenyl-4-hydroxy-cinnamic acid, 2, 2-dimethyl-6-carboxyethenyl-2H-1-benzopyrane, 3, 5-diprenyl-4-hydroxycinnamic acid, 2, 2-dimethyl-6-carboxy-ethenyl-8-prenyl-2H-1-benzopyran [24]. A prenylated cinnamic acid derivative and prenylated tetrahydroxy stilbenes were also reported from the ethyl acetate extract of *Propolis* from Kangaroo Island [25]. Anthraquinones mainly emodin and chrysophanol also have been reported in the ethanolic extract of *Bee Propolis* [26]. Cinnamic acid derivatives also have been reported p-coumaric acid, artepillin C, drupanin, baccharin [27, 28]. A novel prenylated flavonoid was isolated from the Egyptian *Propolis* isonymphaeol-D, along with isonymphaeol-B and nymphaeol-B [29]. During the phytochemical investigation of methanolic extract of the Thai *Propolis* isolation of a new phenylallylflavanone, (7″S)-8-[1-(4'-hydroxy-3'-methoxy-phenyl) prop-2-en-1-yl]-(2S) pinocembrin and (E)-cinnamyl-(E)-cinnamylidenate were reported along with flavonoids and phenolic esters [30].

Presence of two new benzofuran derivatives in the methanolic extract of Brazilian *Propolis* was reported Propolis-benzofurans A and B along with isoprenylated compounds (E)-3-[2, 3-dihydro-2-(1-methylethenyl)-7-prenyl-5-benzofuranyl]-2-propen oic acid and (E)-3-4-hydroxy-3-[(E)-4-(2, 3-dihydrocinnamoyloxy)-3-methyl-2-butenyl]-5-prenylphenyl-2-propen oic acid [31]. During the chemical analysis of water extract from Brazilian *Propolis* a new

compound, propol (3-[4-hydroxy-3-(3-oxo-but-1-enyl)-phenyl]-acrylic acid) were isolated [32].

During the chemical investigation of red-type Mexican *Propolis* three new molecules has *Bee*n isolated, 1-(3', 4'-dihydroxy-2'-methoxyphenyl)-3-(phenyl) propane, (Z)-1-(2'-methoxy-4',5'-dihydroxy phenyl)-2-(3-phenyl) propene and 3-hydroxy-5,6-dimethoxy-flavone, along with known flavanones, isoflavones, and pterocarpans. Isoflavonoids, 1, 3-diaryl propane and 1, 3-diaryl propene carbon skeleton was first time found in Mexican *Propolis* [33].

Glycerol esters derivatives has *Bee*n reported from methanolic extract of Wuhan *Propolis* are 2-acetyl-1-coumaroyl-3-cinnamoyl glycerol, (+)-2-acetyl-1-feruloyl-3-cinnamoyl glycerol, (-)-2-acetyl-1-feruloyl-3-cinnamoyl glycerol, 2-acetyl-1,3-dicinnamoyl glycerol, and (-)-2-acetyl-1-(E)-feruloyl-3-(3″(ζ),16″)-dihydroxy-palmitoyl glycerol [34, 35]. The new esters have *Bee*n isolated from Egyptian *Propolis* are 4-methoxy-hydrocinnamic acid, hydro-ferulic acid, ferulic acid and 2,6-bis-(pentanyloxy)-4-pentanyl phenoxyethanol, were present in a significant amount about 27% [36].

Isolation of Viscidone, vanillin, 3', 4'-(methylendioxy) acetophenone, cinnamic acid, 3-ethoxy-4-methoxy benzaldehyde and 3-methoxy-4-hydroxymethyl ester were first time reported from the Chilean matorral hives [37].

During the phytochemical screening *Propolis* collected from Jeju Island contained chalcon and coumarin compounds (±)-(E)-4'-methoxy-4,2'-dihydroxy-3'-(2″,3″-dihydroxy-3″-methylbutyl)-chalcone, (E,E,E)-4,2',4'-trihydroxy-3'-(7″-hydroxy-3″,7″-dimethyloct- 2″,5″-dienyl)-chalcone, (±)-(E,E)-4,2',4'-trihydroxy-3'-(5″-hydroxy-3″,7″-di-methyl-oct- 2″,6″-dienyl)-chalcone, (±)-(E)-4'-methoxy-4,3″,4″-tri-hydroxy-2″,2″-dimethyl- dihydropyrano-(2',3')-chalcone, (±)-(E)-4'-methoxy-4,3″-dihydroxy-2″-(1‴-hydroxyisopropyl)-dihydro furano-(2',3')-chalcone,(-)-(E)-4,4'-dihydroxy-2″-(1‴-hydroxy-1‴,5‴-dimethylhex-4‴-enyl)-dihydrofurano-(2',3')-chalcone,(+)-(E)-4,2'-dihydroxy-2″-methyl-2″-(3‴,4‴-dihydroxy-4‴-methylpentanyl)-2H-pyrano-(3',4')-chalcone and (-)-(E)-4,2'-dihydroxy-2″-methyl-2″-(3‴,4‴-dihydroxy-4‴-methylpentanyl)-2H-pyrano-(3',4')-chalcone [37] 2',3',4'-trimethoxychalcone, 2'-hydroxy-3',4'-dimethoxy-chalcone, 2',4'-dihydroxy-3'-methoxy-chalcone [38].

From the Argentinean *Propolis* 2',4'-dihydroxy-3'-methoxychalcone, 2',4'-dihydroxychalcone, 2',4',4-trihydroxy-6'-methoxychalcone, 5-hydroxy-4',7-dimethoxyflavone, 4',5-dihydroxy-3,7,8-trimethoxyflavone and 7-hydroxy-5,8-dimethoxyflavone were also been isolated [39]. From the Mexican *Propolis* methanolic extract phenylallylflavanones (2R, 3R)-6-[1-(4'-hydroxy-3'-methoxyphenyl) prop-2-en-1-yl] pinobanksin and (2R, 3R)-6-[1-(4'-hydroxy-3'-methoxyphenyl) prop-2-en-1-yl] pinobanksin 3-acetate were isolated [39, 40].

From Chinese *Propolis* new components 3-O-[(S)-2-methyl-butyroyl] pinobanksin and 6-cinnamyl chrysin were reported from ethyl acetate fraction of the methanolic extract [41]. A novel cinnamate ester derivative benzyl caffeate along with flavonoids 7-O-methyl chrysin, genkwanin and rhamnazin were reported from Liaoxi *Propolis* [42].

Another chemical component which has been isolated from the *Bee Propolis* is terpenes, from the methanolic extract of *Propolis* bicyclic diterpenoids have been isolated and identified as ent-17-hydroxy-3, 13Z-clerodadien-15-oic acid, 15-oxo-3, 13Z-kolavadien-17-oic acid and itd E-isomer kolavadien-17-oic acid [43]. The other derivative compounds reported are isocupressic, communic, imbricatoloic, acetoxy-isocupressic acid and 8(17), 13E-labdadien-15, 19-dioic acid and its methyl ester [44]. Besides this may other prominent compounds were isolated from *Bee Propolis* were the monoterpene α-pinene, the sesquiterpenes β-caryophyllene, α-cubebene, α-muurolene, γ-muurolene, γ-cadinene, germacrene-D, elemol, diterpenes manool and totarol [45].

In recently phytochemical investigation more compounds were reported diterpenes: 14,15-dinor-13-oxo-8(17)-labden-19-oic acid and a mixture of labda-8(17), 13*E*-dien-19-carboxy-15-yl oleate and palmitate, triterpenes, 3,4-seco-cycloart-12-hydroxy-4(28),24-dien-3-oic acid and cycloart-3,7-dihydroxy-24-en-28-oic acid [46].

In a methanolic extract of Jordanian *Propolis* a new lanostane triterpenoid, 24(Z)-1β-3β-dihydroxyeupha-7, 24-dien-26-oic acid, have been isolated 47]. From Indonesian *Propolis* collected East Java, four alk(en) ylresorcinols were reported for the first time from *Propolis*, along with four prenylflavanones and three cycloartane-type triterpenes [48].

From the Methanolic extract of Myanmar *Propolis* thirteen cycloartane-type tritepenes in which two of them is novel (22Z,24E)-3-oxocycloart-22,24-dien-26-oic acid and (24E)-3-oxo-27,28-dihydroxycycloart-24-en-26-oic acid and known four prenylated flavanones were isolated [49, 50]. Isolation of diterpene glycosides ent-8(17)-labden-15-O-alpha-L-rhamnoside and ent-8(17)-labden-15-O-(3'-O-acetyl)-alpha-L-rhamnoside were first reported from the El Salvador *Propolis* [38]. From the Brazilian *Propolis* a novel triterpenoid melliferone and moronic acid, anwuweizonic acid, and betulonic acid were isolated along with aromatic compounds [51]. Isolation of novel compounds 2, 2-dimethyl-8-prenyl-6-vinyl chromene and 2, 6-diprenyl-4-vinyl phenol were reported from the essential oil of Brazilian *Propolis* apart from terpenoids and aromatic components [52, 53].

From the aqueous *Propolis* extract many compounds has been isolation mainly caffeoyl quinic acid derivatives such as methyl 3,4-di-O-caffeoyl quinate, 3,4-di-O-caffeoyl quinic acid, methyl 4,5-di-O-caffeoyl quinate, 3,5-di-O-caffeoyl quinic acid [54] and 3,4-di-caffeoylquinic Acid, is a major component [55-58].

Other compounds reported namely, acetophenones: 2-[1-methyl]-vinyl-5-acetylcumarane 2-[1-hydroxymethyl]-vinyl-6-acetyl-5-hydroxy-cumarane and 2-[1-acetoxymethyl]-vinyl-6-acetyl-5-hydroxycumarane.

Lignans: 1-(4-hydroxy-3-methoxyphenyl)1,2-bis{4-[(E)-3-acetoxy-propen-1-yl]-2 methoxyphenoxy}-propan-3-ol acetate, 1-(4-hydroxy-3-methoxyphenyl)-2-{4-[(E)-3-acetoxypropen-1-yl]-2-methoxyphenoxy}propan-1,3-diol 3-acetate (erythro-and treo), 3-acetoxymethyl-5-[(E)-2-formylethen-1-yl]-2-(4-hydroxy-3-methoxy phenyl)-7-methoxy-2,3-dihydrobenzofuran, sesamin, aschantin, sesartenin, yangambin [58]. Recently two new unknown arylnaphtalene lignans has been isolated, tetrahydrojusticidin B and 6-methoxydiphyllin [59]. Isolation of three novel lignans from Chilean *Propolis* was identified trimeric coniferyl alcohol acetate, diastereomer of the dimeric coniferyl alcohol acetate, dihydrobenzofuran lignan aldehyde with two known lignans [60].

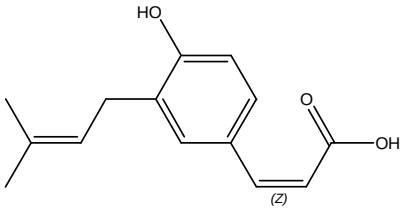
Sugars and sugar alcohols: xylose, galactose**,** mannose, glucuronic acid, lactose, maltose, melibiose**,** erytritol, xylitol, inositol also have been reported isolated from the *Bee Propolis* [61]. From the ethanolic extract of Brazilian green *Propolis,* flavonoids were isolated and purified baccharin, beturetol, kaempferide, isosakuranetin, dihydrokaempferide and drupanin [62, 63]. A prenylated benzophenone was identified from the hexane fraction of Brazilian *Propolis* type 6 hyperibone A [64], hyperibone B, garcinielliptone I along with propolones B, C and D was isolated from Cuban *Propolis* [65]. From the ethanolic extract of Cuban *Propolis* a novel polyisoprenylated benzophenone was isolated [66].

Isolation of new prenylated flavonoid, prokinawan were isolated from *Propolis* collected from Okinawa Japan along with known compounds [67]. It has been reported from Taiwanese *Propolis* isolation of six propolins, A-F and a new propolin G was found which is identical to the Nymphaeol C compound [68]. Isolation of novel compound propolin H from Taiwanese *Propolis* has been reported [69]. Two new prenylflavanones have been isolated from the Taiwanese *Propolis* are propolin A and B [70].

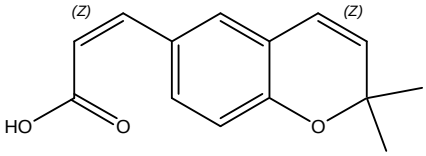
A new Chalcone together with 10 novel open chain neoflavonoids was isolated from the methanolic extract of Nepalese *Propolis* [71].

A Recent investigation carried out by using atomic absorption spectroscopy revealed that the presence of mineral elements in *Bee* Propolis, Ca, Mg, K, Na, Fe and Zn were observed in Macedonian samples [72] and in ethanolic extracts of Cuban samples [73].

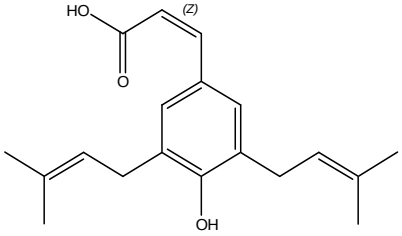
Structure of some molecules isolated from *Propolis*



3-prenyl-4-hydroxycinnamic acid

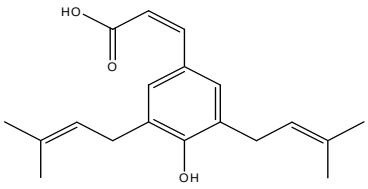


2, 2-dimethyl-6-carboxyethenyl-2H-1-benzopyrane

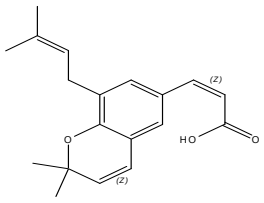


3-(4-Hydroxy-3,5-bis(3-methyl-2-butenyl)phenyl)-2-propenoic acid

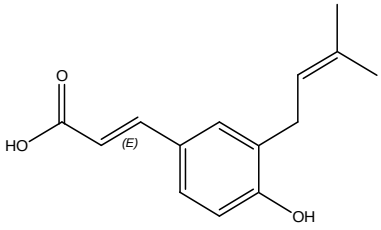
Artepillin C



3, 5-diprenyl-4-hydroxycinnamic acid

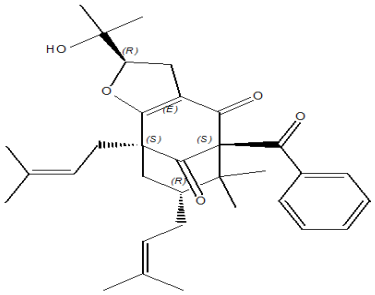


2, 2-dimethyl-6-carboxyethenyl-8-prenyl-2H-1-benzopyran



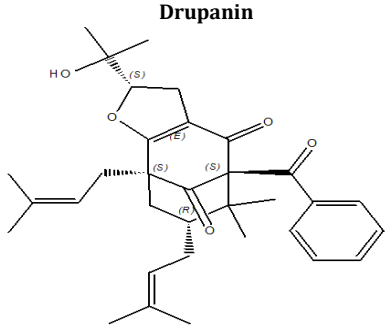
(2E)-3-[4-Hydroxy-3-(3-methyl-2-buten-1-yl)phenyl]acrylic acid

Drupanin



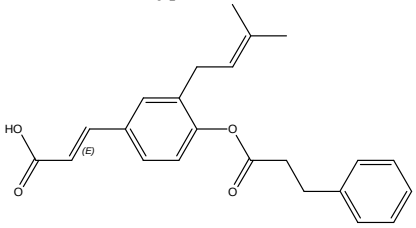
(1S,4R,8S,10R)-8-Benzoyl-4-(2-hydroxy-2-propanyl)-9, 9-dimethyl-1,10-bis(3-methyl-2-buten-1-yl)-3-oxatricyclo[6.3.1.02,6]dodec-2(6)-ene-7,12-dione

Hyperibone B



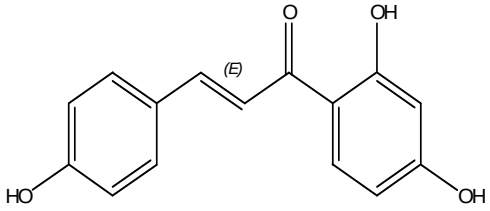
(1S,4S,8S,10R)-8-Benzoyl-4-(2-hydroxy-2-propanyl)-9, 9-dimethyl-1,10-bis(3-methyl-2-buten-1-yl)-3-oxatricyclo[6.3.1.02,6]dodec-2(6)-ene-7,12-dione

Hyperibone A



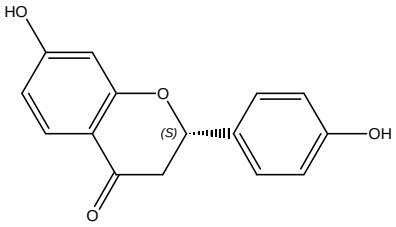
(2E)-3-{3-(3-Methyl-2-buten-1-yl)-4-[(3-phenylpropanoyl)oxy]phenyl}acrylic acid

Baccharin



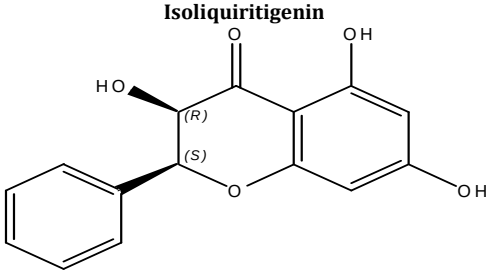
(2E)-1-(2,4-Dihydroxyphenyl)-3-(4-hydroxyphenyl)-2-propen-1-one

Isoliquiritigenin



(2S)-7-Hydroxy-2-(4-hydroxyphenyl)-2,3-dihydro-4H-chromen-4-one

(-)-liquiritigenin



(2S,3R)-3,5,7-Trihydroxy-2-phenyl-chroman-4-one

Pinobanksin

(All structures were draw using ChemDraw ultra-software**)**

CONCLUSION

Propolis has been known at least 300 BC for its traditional medicinal values around the globe. In this review, article data has been thorough collected from various data base study, to sum up the chemical composition of *Propolis* till date. The composition, aroma and color of the *Bee Propolis* vary from hive to hive, season to season, Bee species, botanical source and geographical conditions prevailing at the location from where the resin is collected by honey Bees. Around 500 compounds have been identified till date and the major chemical composition present on *Propolis* are flavonoids, terpenoids, phenolic and their ester. Besides that polyphenols like phenylpropanoids, chalcone, terpenenes, lignans, coumarins, aromatic acids and their esters were also identified and reported from the *Propolis*. However, the other secondary metabolites like as alkaloids, iridoids have not been isolated and identified from *Propolis* till date.

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CONFLICTS OF INTERESTS

There are no conflicts of interest

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