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# Biological properties of propolis extracts: Something new from an ancient product

Nada Zabaiou[a,b,c], Allan Fouache[a,b], Amalia Trousson[a,b], Silvère Baron[a,b], Amar Zellagui[d], Mesbah Lahouel[c,*], Jean-Marc A. Lobaccaro[a,b,**]

[a] Université Clermont Auvergne, GReD, CNRS UMR 6293, INSERM U1103, 28, place Henri Dunant, BP38, F63001, Clermont-Ferrand, France
[b] Centre de Recherche en Nutrition Humaine d'Auvergne,58 Boulevard Montalembert, F-63009 Clermont-Ferrand, France
[c] Laboratory of Molecular Toxicology, Department of Molecular and Cellular Biology, Faculty of Science, Université Mohamed Seddik Ben Yahia, 18000 Jijel, Algeria
[d] Laboratory of Biomolecules and Plant Breeding, Université Larbi Ben M'hidi, 04000 Oum El Bouaghi, Algeria

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ABSTRACT

Natural products are an interesting source of new therapeutics, especially for cancer therapy as 70% of them have botany origin. Propolis, a resinous mixture that honey bees collect and transform from tree buds, sap flows, or other botanical sources, has been used by ethnobotany and traditional practitioners as early in Egypt as 3000 BCE. Enriched in flavonoids, phenol acids and terpene derivatives, propolis has been widely used for its antibacterial, antifungal and anti-inflammatory properties. Even though it is a challenge to standardize propolis composition, chemical analyses have pointed out interesting molecules that also present anti-oxidant and anti-proliferative properties that are of interest in the field of anti-cancer therapy. This review describes the various geographical origins and compositions of propolis, and analyzes how the main compounds of propolis could modulate cell signaling. A focus is made on the putative use of propolis in prostate cancer.



**Contents**



*Abbreviation:* DHT, 5α-dihydrotestosterone; ABCA1, ATP-binding cassette A1; AR, androgen receptor; cIAP-2, baculoviral IAP repeat-containing protein3; Bax, Bcl-2-associated X protein; CAPE, caffeic acid phenethyl ester; ERK, extracellular signal-regulated kinases; IL1-β, interleukin 1-β; LXRs, liver X receptors; MMP, matrix metalloproteinases; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; TLR, toll-like receptor; p70S6K, ribosomal protein S6 kinase beta-1; cTAP-1, transporter associated with antigen processing 1; TNFα, tumor necrosis factor α; TRAIL, tumor necrosis factor related apoptosis inducing ligand; u-PA, urokinase-type plasminogen activator; XIAP, X-linked inhibitor of apoptosis protein.

* Corresponding author at: Université Mohamed Seddik Ben Yahia, Laboratory of Molecular Toxicology, Department of Molecular and Cellular Biology, Faculty of Science, University of Jijel, 98 Ouled Aissa, 18000 Jijel, Algeria.
** Corresponding author at: Université Clermont Auvergne, GReD, 10 Avenue Blaise Pascal, Campus Universitaire des Cézeaux, CS60026, F-63178 Aubiere, France.
*E-mail addresses:* lahouelmesbah@yahoo.fr (M. Lahouel), j-marc.lobaccaro@univ-bpclermont.fr (J.-M.A. Lobaccaro).

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## 1. Introduction

### 1.1. Propolis, an ancient product that has become fashionable

Propolis, also called bee glue is a natural complex matrix that is synthesized by honeybees from products collected in tree buds, saps, resins, mucilages, lattices and other plant sources. The word propolis is derived from Greek, in which pro stands for "at the entrance to" and polis for "city", indicating this natural product is used in hive defense. Due to its waxy nature and mechanical properties, propolis is used by honeybees as cement to keep moisture and temperature stable in the hive all year around, and to seal cracks or open spaces. At elevated temperatures, propolis is soft, pliable and very sticky; however, when cooled, and particularly when frozen or at near freezing, it becomes hard and brittle. It will remain brittle after such treatment even at higher temperatures (Sforcin, 2016).

Since antiquity, mankind has been using propolis in different fields, mainly traditional medicine (Havsteen, 1983; Burdock, 1998). In ancient Greece, propolis was used as a disinfectant and antiseptic for cutaneous and buccal infections. The Egyptians used it mainly to embalm their cadavers. The use of propolis has then been developed over the time. Nowadays, the development of researches on propolis is mainly related to the development of chemistry and analytical methods that allowed analyzing its chemical composition.

The composition of propolis depends on the source of the various trees used by honeybees: generally poplar trees in the temperate zones, Betula in the Northern, Dalechampia in the Equatorial regions, Clusia in Venezuela and Xanthorrhoea in Australia (Burdock, 1998). Chemical heterogeneity of propolis is thus easily understandable as it is a complex mixture of compounds derived from various plants and processed by salivary enzymes of bees. Hence, composition of propolis depends of the plants, the seasons resins are collected, and the bee species. This chemical diversity brings a crucial question of standardization, even though bees, by themselves, do not change its chemical composition (Bankova et al., 2000).

### 1.2. Composition of propolis

As presented above, various types of propolis have been reported according to the geographical areas of production, botanical sources and chemical compositions (Bankova, 2005a). The temperate zone propolis is generally referred as poplar propolis because mainly produced from the bud exudates of *Populus* trees (Popova et al., 2004). Birch propolis is found specifically in Russia and is different from poplar propolis (Christov et al., 2006). Pacific propolis is a type of propolis found in Taiwan, Japan and Solomon Island (Popova et al., 2009). Various forms of Brazilian propolis are available: green propolis is derived from *Baccharis dracunculifornia* (Righi et al., 2011) while brown propolis comes from *Copaifera* species (Sawaya et al., 2006) and red propolis is obtained from *Dalbergia ecastophyllum* (L) (Piccinelli et al., 2011).

#### 1.2.1. Gross composition of propolis

Propolis sample analyses from various parts of the world have been collectively reported to contain over 300 different chemical compounds (Huang et al., 2014). Raw propolis is typically composed of 50% plant resins, 30% waxes, 10% essential and aromatic oils, 5% pollens and 5% other organic substances (Bankova, 2005a). Through various high throughput technics such as mass spectroscopy, nuclear magnetic resonance, gas chromatography coupled with mass spectroscopy, it has been possible to identify several families of chemically active compounds (For a review (Bankova, 2005b)) but not to define a minimal common composition with clear concentrations of the various compounds. Nevertheless, the main chemical groups present in propolis resin comprise phenolic acids or their esters, flavonoids, terpens, aromatic aldehydes and alcohols, fatty acids, stilbens and β-steroids (Watanabe et al., 2011).

Flavonoids are the main compounds of propolis as they are responsible for the main pharmacological (see below). Among them it could be found flavones (luteolin), flavonols (quercetins and derivatives), flavanones (pinocembrin, or 5,7-dihydroxyflavone, and derivatives, and naringenin), flavanonols (garbanzol and alnustinol), chalcones and dihydrochalcones, isoflavones (calycosin), isodihydroflavones (daidzein), flavans, isoflavans (vestitol and derivatives) and neoflavonoids (homopterocarpin and medicarpin) (for an extended review (Bankova, 2005b)).

Terpenoids, even though presented in only 10%, are responsible for the odor, because they are volatile components of plants, and also contribute for the biological properties of propolis. Terpenoids include monoterpenes (terpineol, camphor), diterpenes (the main group, such as ferruginol, junicedric acid and derivatives, pimaric acid, totarolone), triterpenes (such as lupeol and derivatives, lanosterol, amyrone and derivatives) and sesquiterpenes (such γ-elemene, valencene, α-ylangene, α-bisabolol) (Table 1).

Phenolic compounds include various acids such as cinnamic, p-coumaric, chicoric, caffeic and fulric acids (For a review (Bankova, 2005b)).

#### 1.2.2. Geographical origin of propolis and composition

This overview of propolis composition obviously depends of the area of collection. For example propolis samples from Europe, North America and other temperate zones are mainly composed of flavonoids (pinocembrin, pinobanksin, quercetin, chrysin and galangin), phenolic acids and their esters (Falcão et al., 2010), likewise poplar propolis (Falcão et al., 2010; Sun et al., 2012).

Mediterranean propolis is characteristic by the high concentration of terpenoids and is found in many regions like Greece (Popova et al., 2010; Celemli et al., 2013), Switzerland (Bankova et al., 2002), Malta (Popova et al., 2011), Turkey (Duran et al., 2011; Silici et al., 2007) and Algeria (Piccinelli et al., 2013). Among these, Algerian one is derived from two principal species *Populus spp* and *Citrus spp* and is composed of pinocembrin, chicoric and caffeic acids and their esters, galangin (Boutabet et al., 2011), diterpenic acids, flavonols like chrysin, and aromatic acids (Piccinelli et al., 2013). In Greece, propolis is rich of flavonoids and diterpenic acids (Popova et al., 2010). *Populous spp* and *eucapyptus* are the main plant sources of Turkish propolis. Its composition is not different from that of Algeria and Greece with caffeic acid and its esters, pinobanksin, pinocembin, diterpenic acids, aromatic acids and flavonols (Duran et al., 2011).

Many studies with African propolis from different regions like Kenya, Cameroon, Congo and Ethiopia, showed that triterpenoids