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Matricaria recutita and its Isolate-Apigenin: Economic Value, Ethnopharmacology and Chemico-Biological Profiles in Retrospect

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Review Article

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ABSTRACT

Background: The collection, processing, preservation, storage and intended use could change or influence the value of botanical material. The aspects of biological activities are often neglected in the assessment of economic value of botanical materials and their isolates. *Matricaria recutita* L. popularly known as chamomile is widely acclaimed as "capable of anything" or as a "cure all" species (alles zutraut). As an exotic plant in many parts of the world, its easy of cultivation offer opportunity for its development on industrial scale product.

Objective: This review focus on biological activities of and industrial values of *M. recutita* and its isolate - apigenin as an important biomarker of this species.

Methods: Bibliographic searches of scientific journals, books, electronic sources, unpublished theses and electronic databases such as ScienceDirect, PubMed, etc. were conducted.

Results: Findings showed that *M. recutita* is a multipurpose species with wide range of therapeutic potentials. Some of the widely acclaimed biological activities of this species are traceable to apigenin. Despite the numerous pitfalls in associating biological activity to a specific isolate, the active principle apigenin has been reported as a biomarker of *M. recutita*. The susceptibility of apigenin to chemical modifications offers enormous opportunity for industrial developments.

Conclusion: This review provides scientific data for future consultation and economic exploration of *M. recutita* and apigenin.

INTRODUCTION

Over the years, the economic values of medicinal plants are widely associated with the local perceptions and popular applications [1]. The collection, processing, preservation and intended use could change the value of botanical material. A value chain of botanical has been described as the sequence of activities required to make a finished product from its initial starting material [2]. However, the aspect of biological activities is often neglected in the assessment of economic value of botanical materials and their active metabolites. Hence, this review focuses on biological activities and industrial values of *M. recutita* and its isolate-apigenin as an important biomarker of this species.

Botany

As a member of Asteraceae (compositae) family [3], *M. recutita* popularly known as chamomile is widely represented by two known varieties viz. German chamomile (*Matricaria chamomilla*) and Roman chamomile (*Chamaemelum nobile*). It is important to

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highlight the controversial nomenclature as a result of the mistakes that were made by Linnaeus in the first edition of his "Species Plantarum" which he later corrected [4]. The best-known botanical name for true chamomile is *M. recutita* [(syn. *M. chamomilla*, *Chamomilla recutita* (L.) Rauschert, belonging to the genus *Chamomilla* and family Asteraceae [5]]. *M. recutita* is a diploid species (2n=18), allogamous in nature, exhibiting wide segregation as a commercial crop [4]. *M. recutita* is the most common variety being used for medicinal purposes. *M. recutita* has thin spindle-shaped roots with branched erect stem and a height 10 cm to 80 cm [4]. The long and narrow leaves are bi- to tripinnate. The flowers of *Matricaria* can be differentiated from those of the English Chamomile by their hollow receptacle (6 mm to 8 mm wide, flat in the beginning and conical, cone-shaped later), and without paleae. This is a very important distinctive characteristic of *Matricaria*. The capitulum spreads out to 10 mm to 17 mm in diameter and consists of an involucre, up to 20 marginal ligulate florets and many tubular florets. Comparatively, *Matricaria* has smaller flower heads than chamomile. The flower heads are placed separately, they have a diameter of 10 mm to 30 mm, and they are pedunculate and heterogamous [4]. The golden yellow tubular florets with 5 teeth are 1.5 mm to 2.5 mm long, ending always in a glandulous tube. The 11-27 white plant flowers are 6 mm to 11 mm long, 3.5 mm wide, and arranged concentrically. It has a bitter and aromatic taste but the odour is usually weaker than that of Roman chamomile. The fruit is a yellowish brown achene [4].

Ethnopharmacology

M. chamomilla was considered a sacred gift from the sun god by the ancient Egyptians. Chamomile is a well-known old time and widely use drug with diverse common names including Baboonig, Babuna, Babuna camornile, Babunj, German chamomile, Hungarian chamomile, Roman chamomile, English chamomile, Camomilla, Flos chamomile, Single chamomile, sweet false chamomile, pinheads, and scented mayweed [6,7]. The Europeans considered this species a "cure all", while it is referred to as "alles zutraut", meaning "capable of anything" in Germany [8]. This species has been used for centuries as a medicinal plant for external wounds, gastrointestinal ailments, eczema, gout, skin irritations and emotional problems, neuralgia, sciatica, rheumatic pain, hemorrhoids, mastitis, leg ulcers, diaper rash, cracked nipples, chicken pox, poison ivy, conjunctivitis, inflammation of the skin, mucous membranes, ano-genital area, bacterial skin diseases, including those of the oral cavity and gums, respiratory tract inflammation, deodorant, bacteriostatic, antimicrobial, anticatarrhal treatment [9-12]. It is also used to treat central nervous system related disorders such as anxiety, hysteria, nightmares, insomnia and other sleep problems, convulsions, and even delirium tremens, spasm [11-13]. This species is also known for its usage as a hair tint and conditioner, digestive aid to treat flatulence, indigestion, diarrhea, anorexia, motion sickness, nausea, vomiting and treatment of malaria and parasitic worm infections, cystitis, colds, and flu [14,15].

Economic Values and Potentials

M. chamomilla is an annual plant. It has been used as an herbal tea or supplementary food all over the world. It is one of the well-documented medicinal plants in the world [16] and it is included in the pharmacopoeia of 26 countries [16]. The plant possesses great economic value and is in great demand in the European countries because of its numerous pharmacological properties [4]. In Germany, chamomile sales exceeded $8.3 million in 1996 [17] and more than 4,000 tons of chamomile are produced yearly [18]. It grows indigenously in Europe, North West, Asia, North Africa, and cultivated in North America, South America and in many parts of the world [4,19]. Flowers of this species are exported to Germany in bulk for distillation of the essential oil [20].

In South Africa, the essential oil yield of 1 to 4 kg/ha can be expected from chamomile. In 1995, the world production was estimated to be approximately 500 tons of dried flowers per annum, from large scale farming [21]. By 1998 (three years after), the production has by far doubled (1000 tons of dried flower per annum) due to huge investment in large-scale farming. Dried flower yield can vary, depending on time of planting, soil, climate, rainfall and irrigation. Between 2 and 6 tons of dry flowers can be harvested per hectare [21]. Chamomiles are grown commercially in Europe and the former USSR (Belarus, Ukraine, Moldova,) North Caucasus to South Siberia, North and East Africa (Egypt, Ethiopia), Asia (Turkey, Afghanistan, Pakistan, North India, and Japan), North and South America (East Coast of the USA, Cuba, Argentina, and Brazil) and New Zealand [21]. This species stands out as the most cultivated medicinal plant in the world [22]. The State of Paraná in Brazil is the pioneer in the growing of this species. The city of Mandirituba is the site for the largest national production in Brazil [23,24]. Chamomile requires cool, temperate conditions to grow well (temperatures range of 7 °C to 26 °C are required). To be able to grow well vegetatively and produce abundant flowers, chamomile needs long summer days, full sun and high heat units to produce optimum oil yields. Chamomile is drought tolerant; an annual precipitation of 400 mm to 1400 mm per season is enough to produce a good crop. This species can be grown on a wide range of soil types, but prefers a well-drained, sandy or sandy-loam soil with a pH of 4.8 to 8.3 [21].

Biological Activities of *M. recutita*

Biological activities of this species include anti-inflammatory, immunomodulatory, arcaricadal, antihyperglycemic, anticancer, antimicrobial, antiulcer, anti-pruritic, anti-allergic, anti-osteoporosis. This species is being used for the treatment of oral mucositis, intracanal irrigant, infant botulism and for wound healing. The lousicidal, uterotonic, ovicidal, repellent, virucidal, anti-stress, antidepressant and anxiolytic properties have also been reported [10]. Chamomile is generally safe for consumption, although patients with hypersensitivity to ragweed and other members of the compositae family should use with caution. Allergic reactions to chamomile are rare and no potentially toxic compounds have been reported [25].

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Industrial Values and Products

The essential oils extracted from fresh or dried flower heads of this plant have flavouring and colouring properties and these properties are widely used in industry for commercial products like soaps, detergents, perfumes, lotions, ointments, hair products, baked goods, confectioneries, alcoholic beverages and herbal teas [10]. Kamillosan, a chamomile mouthwash industrial product, has been used by European oncologists to treat chemotherapy-induced mouth sores [25]. Most of the pharmaceutical value of the plant lies in its characteristically blue coloured volatile oil (up to 1.5%). Chamomilla crude extract has an amber to brown limpid to opalescent liquid **(Figure 1)** that has a characteristic odor. The extract can be obtained from the powdered flower extracted in propylene glycol/water solvent mixture. Different biocosmetic products in form of body and hand lotions, face and neck preparations, and other skin care preparations can be produced. Basic equipment for grinding, percolation and spray drying as shown in **Figure 1** have been widely used for the processing of chamomile and other botanicals.

Figure 1. Illustration of processes and equipments for the micro-extraction of crude extract from chamomile flowers.

Other typical products include tea or infusion with adult dose consisting of 150 cc of boiling water over 3 g fresh flower heads, steep for 5 to 10 minutes; drink three times daily [11]. Alcoholic liquid preparation of 1:1 w/v (45% alcohol) to be taken three times daily (1 ml to 4 ml) [11] and other standardized preparations of chamomile are available. Examples include Nutritional Dynamics German Chamomile, 400 mg chamomile flower per capsule (standardized to 1% apigenin, 0.5% essential oil); Nature's Way German Chamomile, 125 mg extract (standardized to 1.2% apigenin); Nature's Way German Chamomile, 350 mg chamomile flower per capsule (0.5% essential oil potency guaranteed) [17].

Constituents of *M. chamomilla*

M. chamomilla contains a large number of therapeutically interesting and active classes of compounds: mucins, sesquiterpenes, coumarins, polyacetylenes, phenyl carboxylic acids, amino acids, phytosterols, choline, mineral substances and flavonoids [4]. The bioactive phenolic compounds including herniarin and umbelliferone (coumarin), chlorogenic acid and caffeic acid (phenylpropanoids), apigenin, apigenin-7-O-glucoside, luteolin and luteolin-7-O-glucoside (flavones), quercetin and rutin (flavonols), and naringenin (flavanone) have been reported in chamomile extract [26]. The coumarins herniarin, umbelliferone, and esculetin make up approximately 0.1% of the total constituents. Some of the activity related compounds in *M. chamomilla* are flavonoids and polysaccharides [27,28]. The major flavonoid components are apigenin, luteolin, and quercetin, which comprise 16.8%, 1.9% and 9.9%, respectively, of total flavonoids [29]. In natural conditions, most of the flavonoids occur as glycosides bound to the sugar moiety and are highly stable and water-soluble. Thus, chamomile is one of the richest dietary sources of apigenin (840 mg/100 g in contrast to 9 mg/100 g present in peppermint), a flavone that is extracted from the ligules for commercial use [29]. This flavonoid is soluble in hot water, and the amount obtained from frequent consumption of tea is not negligible. The lipophilic constituents of this species include, phytosterols, lipidic and waxy substances while the hydrophilic constituents consist of choline, amino acids, mucin, mineral substances, phenol carboxylic acids and flavonoids [30,31]. The major components of the essential oil are terpenoids: (-)-α-bisabolol α-bisabolol oxide A and B, chamazulene, sesquiterpenes including α-farnesene, and the yield of the essential oil from the flowers is about 0.4% [31] **(Table 1)**.

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Table 1. Other plant species containing apigenin.

Family	Species	Common/popular name	Distribution	References
Asteraceae	*Achillea millefolium* L	Yarrow	Northern hemisphere	[32-38]
	Chamaemelum nobile L	Perennial chamomile, Roman chamomile	Sub-oceanic Southern Temperate	
Apiaceae	*Apium graveolens* L	Celery	Tropic and sub-tropic countries	[39-41]
Theaceae	*Camellia sinensis* L	Tea	Tropical and subtropical areas	[42,43]
Umbelliferae	*Coriandrum sativum* L	Cilantro	Italy, India, Morocco, and Eastern Europe	[44-46]
Plantaginaceae	*Digitalis purpurea* L	Purple foxglove	Temperate Europe	[47-49]
Asteraceae	*Echinacea* spp.	Coneflower	Atlantic drainage region of the United States, extending into south central Canada	[50,51]
Ginkgoaceae	*Gingko biloba* L	Gingko		[49,52]
Fabaceae	*Glycyrrhiza glabra* L	Liquorice, Licorice	Spain, Italy, Turkey, Israel, Syria, Iran, China and Russia	[53-55]
Linaceae	*Linum usitatissimum* L	Flax	Temperate climate zone	[56-59]
Lamiaceae	*Marrubium vulgare* L	Horehound	Temperate regions of Europe, northern Africa and Asia	[60-63]
Asteraceae	*M. recutita* L (syn: *M. chamomilla*; M. *suaveolens*; Hungarian chamomile; German chamomile; *Chamomilla chamomilla*; *Chamomilla recutita*)	Annual chamomile	Europe, North and South America	[16,29,64-68]
Lamiaceae	*Mentha spicata* L	Spearmint	Britain and other European countries	[69-71]
Labiatae	*Ocimum basilicum* L	Basil	Tropical regions of Asia, Africa, and Central and South America	[72-75]
Lamiaceae	*Origanum vulgare* L	Oregano	Eurasia, North Africa, North America	[76]
Passifloraceae	*Passiflora tripartita*	Banana Passion fruit	temperate and tropical South America	[77,78]
Passifloraceae	*Passiflora incarnata* L	Maypop, Maracuja or Passion flower	temperate and tropical South America	[79-85]
Passifloraceae	*Passiflora edulis*	purple form (*P. edulis* Sims) and the yellow form (*P. edulis var. flavicarpa* Degenerer)	Warm and tropical regions of America, Southeast Asia and Australia.	[86-89]
Compositae	*Onopordum illyricum* L	Cardo maggiore (Italy)	Mediterranean coast of Italy	[90-92]
Goodeniaceae	*Scaevola sericea* V	Beach naupaka		[93]
Solanaceae	*Capsicum annuum*	Chili pepper		[93-95]
Fabaceae	*Medicago sativa* L	Alfafa	Native to warmer temperate climates	[96,97]
Acanthaceae	*Asystasia gangetica*	Chinese violet	Tropical regions	[93,98-100]
Apiaceae	*Petroselium crispum*	Parsley	Native to Europe and may be found in other parts of the world including North America.	[93,101,102]
Lamiaceae	*Thymus vulgaris*	Thyme	Native to southern Europe from the western Mediterranean to southern Italy	[102-104]
Labiatae	*Rosmarinus officinalis*	Rosemary	Mediterranean basin	[93,105]
Asteraceae	*Vernonia hymenolepis*	Sweet bitter leaf	Sub-Saharan Africa	[93]
Scrophulariaceae	*Russelia equisetiformis*		Native to Mexico and Guatemala	[106]
Asteraceae	*Vernonia amygdalina*		Tropical Africa	[107]
Asteraceae *Garcinia kola*	*Vernonia scorpioides* L	Known in Brazil as Piracá, Enxugaor Erva-de-São-Simão	Occupies regions of great climatic variations	[108,109]
Passifloraceae	*Passiflora foetida*	Weed passion flower	tropical regions and rain forests of South America	[93,110,111]

Apigenin

Apigenin, a flavonoid **(Figure 2)** is a naturally occurring polyphenol. There are four major classes of flavonoids: the 4-oxoflavonoids (flavones, flavonols, etc.), anthocyanins, isoflavones, and the flavan-3-ol derivatives (catechin and tannins) [112].

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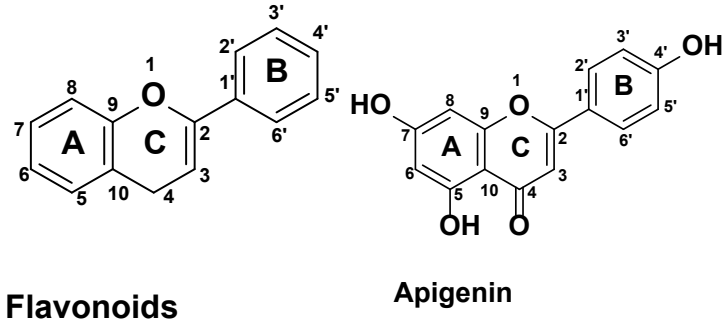


Figure 2. Basic structure of flavonoids and apigenin.

Apigenin (4',5,7-trihydroxyflavone), has been considered as a biomarker of chamomile. By definition, chemical biomarker is a substance or chemical group that can be analyzed with column chromatography, HPLC, gas chromatography and are present in large quantity and, in preference, responsible for the pharmacological activity of medicinal plant [113]. According to WHO and National Agency of Sanitary Surveillance (ANVISA), the utilization of chemical biomarker in quality control and standardization of phytotherapy products are basic requirements [114]. The preference for Apigenin in the current review does not necessarily exclude the importance of other constituents that are present in. In fact, the synergism among constituents of chamomile is responsible for most of its economic or biological values.

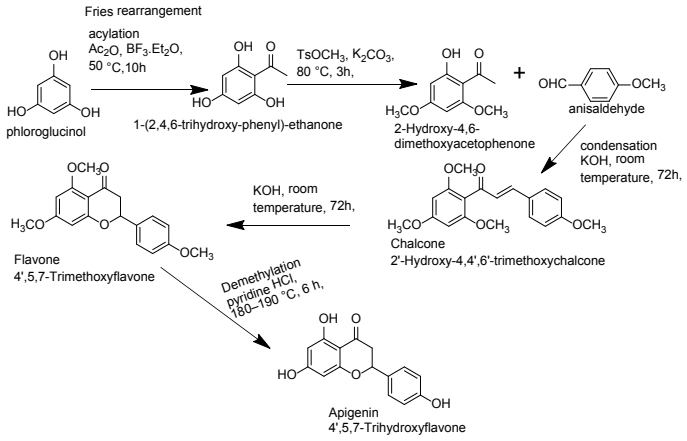
Apigenin possesses a variety of biological activities, such as free radical scavenging, antioxidantive, pro- or anti-mutagenic, anti-inflammatory, antiviral, or purgative effects [115,116]. In addition to chamomile tea [29], other sources of apigenin are as contained in **Table 1** include grapefruits, onions, oranges and some spices such as parsley [117], celery, yarrow, tarragon, cilantro, foxglove, coneflower, licorice, flax, passion flower, horehound, spearmint, basil, and oregano [48,49], red wine [118], beer [119] and *Gingko biloba* [49].

Physical and Chemical Properties of Apigenin

Apigenin is a colouring compound of plant extracts. Vegetal yellow dyes are flavonoids compounds and notably both luteolin and apigenin (1) which are largely found in *Reseda luteola*, *Genista tinctoria*, *Solidago* spp. and *M. recutita*. Apigenin ($C_{15}H_{10}O_5$, Mol. wt.: 270.24) has yellow needles, with melting point of 347.5°C [120], practically insoluble in water, moderately soluble in hot alcohol, soluble in dilute KOH. The active apigenin is often found in the form of various acylated derivatives and Apigenin-7-O-glucoside [121]. The aglycone form of apigenin **(Figure 1)** consist of a benzene ring (A) condensed with a six-membered ring (C) which carries a phenyl group (γ-pyrone ring) (B) as a substituent in the 2-position.

Synthesis of Apigenin

In addition to naturally occurring apigenin, this molecule has been synthesiszed from phloroglucinol 2 in five steps as shown in **Scheme 1** with 40% yield and through microwave irradiation of phloroglucinol and β-ketoesters with a yield of 81% [122].



Ac_2O: Acetic Anhydride; $TsOCH_3$: Methyl p-Toluene Sulfonate; K_2CO_3: Potassium Carbonate; KOH: Potassium Hydroxide; DMSO: Dimethyl Sulfoxide; HCl: Pyridine Hydrochloride [123]

Scheme 1. Biosynthetic pathway of apigenin from phloroglucinol.

Abbreviations: acetic anhydride (Ac_2O), methyl p-toluene sulfonate ($TsOCH_3$), potassium carbonate (K_2CO_3), potassium hydroxide (KOH), Dimethyl sulfoxide (DMSO), pyridine hydrochloride (HCl) [123].

Biosynthesis pathway of apigenin from tyrosine has been achieved in *Escherichia coli*. The p-coumaric acid formed through the activitiy of tyrosine ammonium lyase on tyrosine was further converted by four enzymes (4CL, CHS, CHI, and FNS; **Scheme 2**)

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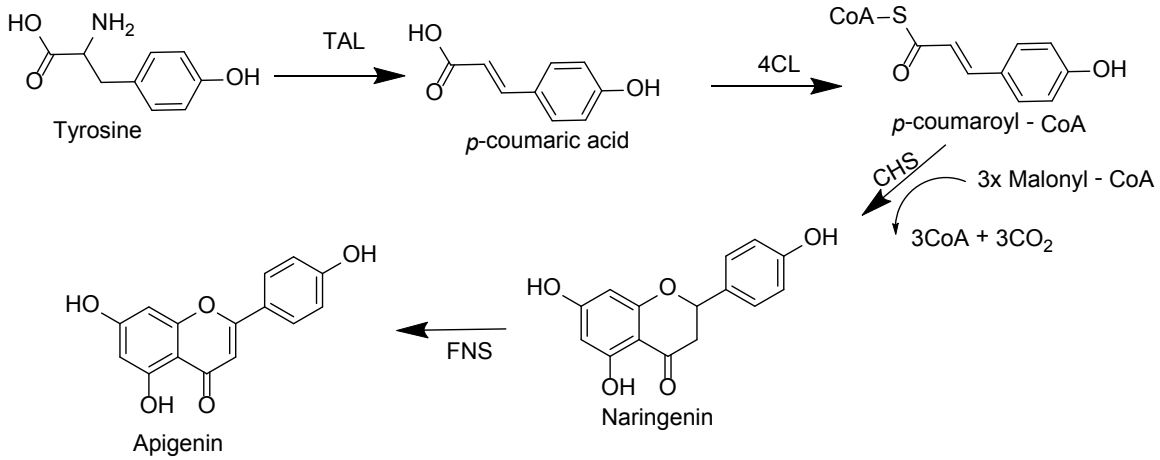
to apigenin. Modification of apigenin has been widely reported in literature [124].



TAL: Tyrosine Ammonium Lysate; 4CL: 4-coumarate CoA Ligase; CHS: Chalcone Synthase; FNS: Flavone Synthase; POMT7: Apigenin 7-Omethyltransferase

Scheme 2. Biosynthetic pathway of apigenin from tyrosine.

Industrial Application of Apigenin

The manufactures offer plant dye extracts, powder pigments and pigment pastes for use in hair colouring, hair highlights and textile industry [125]. The plant dyes, which meet the growing needs of hair care formulations, such as dyes, shampoos and conditioners, were designed as part of a new range of "environmentally responsible" cosmetic ingredients. Vegetal yellow dyes are flavonoids compounds and notably are both luteolin and apigenin [126,127]. According to the literature, the most accepted hypotheses for this effect of chamomile extracts are based on the deposition of its active principle, the apigenin which is responsible for the yellow pigmentation of hair, i.e., yellowish coloration [128]. In addition, apigenin promotes hair growth, hence, it can be useful as an adjunctive therapy for the treatment of androgenetic alopecia [129,130].

BIOLOGICAL ACTIVITIES OF APIGENIN

Anticancer

Apigenin, has been reported to suppress proliferation in a wide variety of solid tumors and hematological cancers [131]. Its anticancer properties have been extensively studied *in vitro* and *in vivo* [48,132]. It can enhance gap-junction intercellular communication, inhibits growth, arrest cell cycle and induce apoptosis of human prostate cancer, breast cancer and leukemia [115,125,133-138]. Nabavi et al. [125] have shown that apigenin has the ability to induce anticancer effect through 4 different mechanisms: 1) induction of extrinsic apoptosis, 2) inhibition of aromatase, fatty acid synthase, and MAPK, 3) suppression of angiogenesis through down-regulation of NF-kB and VEGF, 4) down-regulation of PI3K/AKT pathways and ErbB2 expression. Apigenin can also modulate activities of cytochrome P450 monooxygenase (P450)2 1A, an isoform involved in bioactivation of numerous carcinogens [139], and it is a ligand of estrogen receptor [132,140]. This flavonoid was shown to inhibit the proliferation of keratinocytes). It was also described as a preventive agent in mouse skin tumorigenesis [48].

Caltagirone et al. [141] found that the conjugation of quercetin with apigenin inhibit melanoma growth and invasive and metastatic potential; therefore, they may constitute a valuable tool in the combination therapy of metastatic melanoma. Choudhury et al. [142] reported that conjugation between apigenin and curcumin induced cell death of lung cancer cells. These two compounds bound different sites on tubulin, inhibited its polymerization into microtubule, which might cause apoptosis in cancer cells.

Antimicrobial

Apigenin was shown to be a cariostatic agent, based on its ability to inhibit glucosyltransferases; it is a promising anticaries compound. Apigenin effectively inhibited the synthesis of glucan at levels never observed before; it may influence the chemical and microbial composition of human dental plaque. Propolis or its constituents offer a very attractive route to identify new agents to reduce dental caries and plaque formation [143].

Carvalho et al. [144] showed that the crude ethanolic extract of *M. chamomilla* L. flowers, which contains apigenin, caused growth inhibition of *Pseudomonas aeruginosa* in broth dilution, and was confirmed by agar diffusion (10 mm diameter inhibition zone).

Anxiolytic

Viola et al. [64] studied activities of apigenin from aqueous unstandardized fraction of chamomile extract and found that it has an anxiolytic activity in mice without demonstrating sedatve or muscle relaxant effects. Kumar et al. [145] also found that

apigenin is responsible for the anxiolytic activity of *Turnera aphrodisiaca*. Apigenin also have been shown to reduce γ-aminobutyric acid-activated chloride currents and also to reduce locomotor activity of rats. Many studies have shown the anxiolytic activity of apigenin in rats, by binding to benzodiazepine receptors and reducing GABA-activated activity [28,65,146-148].

Antidepressant

Li et al. [149] showed that apigenin has an antidepressant-like effect in lipopolysaccharide (LPS) -induced mouse model of depression. The mechanism for this effect might be related to the inhibition of inflammatory cytokines, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) expression via the modulation of nuclear factor-B (NF-B) activation [150].

Antioxidant

Flavonoids can act as antioxidants, through free radicals mediated reactions by inhibiting biomolecules from undergoing oxidative damage [151]. They can also act directly by quenching reactive oxygen species, inhibiting enzymes, chelating metal ions (Fe^{3+}, Cu^{+}), promoting radical production, and regenerating membrane-bound antioxidants such as α-tocopherol. Their beneficial effects are related to diseases in which oxidative processes are remarkable such as atherosclerosis, coronary heart disease, certain tumors, and aging itself [152].

Leopoldini et al. [153] showed how the functional groups of apigenin can affect its radical scavenging activity. On the basis of the results obtained the ortho-dihydroxy structure in the B ring which confers high stability to the radical species through H-bond formation and the C2-C3 double bond in conjugation with the 4-oxo function in the C ring, which is responsible for the electronic delocalization starting from the B ring are important to radical scavenging activity. Unlike apigenin (with BDE of 82.20 kcal/mol), flavonoids with the dihydroxy functionality are the most active in donating an H atom, as confirmed by their low BDE values (e.g., Luteolin with BDE of 74.54 kcal/mol). The planar conformation and the extended electronic delocalization between adjacent rings of apigenin determine low IP value (176.05 kcal/mol). Gas-phase BDE and IP have been considered as excellent primary indicators of free radical scavenging activity [153].

Neuroprotective

Apigenin has a high distribution level in the brain [154,155] which provides a solid evidence of its neuroprotective action. Zhao et al. [156] showed that apigenin could exert neuroprotection against Ab-induced toxicity in the presence of copper mainly through the mechanisms that regulate redox imbalance, preserve mitochondrial function, inhibit MAPK pathways, and depress neuronal apoptosis.

Ha et al. [157] proved that apigenin protected neurons from the injury in middle cerebral artery occlusion in rats. Apigenin also improved the neurological recovery after spinal cord injury [158], displaying its neuroprotective and neurotrophic effects in some neurological diseases [158,159].

One of the mechanisms already described for the neuroprotective activity of apigenin is that it inhibits the toll-like receptor 4-mediated inflammatory pathway and protects the integrity of blood-brain barrier against early brain injury after subarachnoid hemorrhage [160]. Other studies have reported that apigenin regulated nitric oxide production through the regulation of NF-Kb and inhibition of tumor necrosis factor in mouse cell lines [161].

Apigenin and luteolin treatment showed to improve the locomotor and muscular activities in induced Parkinsonism in mice which means they protected the dopaminergic neurons probably by reducing oxidative damage, neuroinflammation and microglial activation along with enhanced neurotrophic potential [159]

Anti-Chikungunya

Pohjala et al. [162] found that natural compounds with a 5,7-dihydroxyflavones structure, such as apigenin, were found to suppress activities of Enhanced Green Fluorescent Protein (EGFP) and Renilla Luciferase (Rluc) marker genes expressed by the chikungunya virus replicon. According to Murali et al. [163] apigenin and luteolin rich ethanolic fraction from Cynodon dactylon is a potential therapeutic agent against chikungunya virus infection as the fraction inhibits the virus activity and does not show cytotoxicity *in vitro* using Vero cells.

Anti-Inflammatory

Apigenin can modulate the action and the production of inflammatory molecules by modulating the action of other molecules [10]. Its anti-inflammatory effect is exerted by inhibiting NF-κB signaling pathway in several disease models [164,165]. Choi et al. [166] found that this flavonoid has a powerful anti-inflammatory activity by inhibiting inducible nitric oxide synthase (iNOS), nitric oxide (NO) production and cyclooxygenase-2 (COX-2) expression.

Downmodulation of TNF-α (tumor necrosis factor) by apigenin has been reported *in vitro*. Apigenin has been shown to inhibit TNF-α-induced NF-kB-mediated transactivation of a luciferase reporter gene. It can also decrease H5N1-induced production of IL-6, IP-10, and TNF-α in influenza A virus-infected cells [167]. This flavonoid can reduce TNF-α significantly in THP1 macrophages [168] and inhibit expression of TNF-α and IL-6 by inhibiting NF-κB activation in mouse peritoneal macrophages [169]. It has been

shown that apigenin also inhibited TNF-α, iNOS mRNA, and iNOS protein in RAW cells [170]. And also this polyphenol suppresses expression of TNF-α, IL-8, IL-6, Granulocyte macrophage colony-stimulating factor (GM-CSF), and COX-2 by decreasing intracellular Ca2+ level and inhibiting NF-κB activation in HMC-1 cells [171].

Downmodulation of TNF-α by apigenin has also been reported *in vivo*. It inhibits production of TNF-α, IL-1b, IL-6, and IL-33 in mice [172], decreases the levels of TNF-α, IL-1b, and IL-6 in gamma-irradiated mice [173], and also attenuates TNF-α-induced vascular cell adhesion molecule (VCAM-1) mRNA and protein expression in hypertensive rats [174].

Other Reported Activities

Some compounds called 5,7,4-hydroxyflavonoids, such as apigenin, have been shown to possess estrogenic or antiestrogenic properties *in vitro* [48,116,175] as well as *in vivo* [33, 175,176] has reported that estrogen receptors, α and β, can be activated by apigenin *in vitro*. Vasodilatory effect of apigenin has also been reported by Ko et al. [40] in rats. The mechanism by which it happens is that it relaxes rat thoracic aorta by suppressing the Ca^{2+} influx through both voltage- and receptor-operated calcium channels.

A wide variety of biological activities including anti-oxidation, anti-inflammation, anti-platelet, anti-thrombotic action, anti-allergic, inhibitor of lypoxygenase, cyclooxygenase, cytotoxicity among others have been reported in species on **Table 1**.

PHARMACOKINETICS AND TOXICOLOGY ASPECTS

The economic and therapeutic value of apigenin make the knowledge concerning its metabolism and its pharmacokinetics a necessity. The UDP glucuronosyltransferase UGT1A1 rapidly metabolizes apigenin into luteolin, conjugated derivatives (glucurono- and sulfoconjugates - hydrophilic metabolites) that are subsequently excreted in the urine; the fraction of apigenin intake excreted being 0.58% [49,177]. According to Griffiths and Smith [178], *in vivo* metabolism studies showed that maximal excretion of apigenin and its metabolites occurred between 48 and 72 h of oral administration and that derivatives were all conjugated compounds. Apigenin is detected in the blood after 24 hours of initial ingestion with a half-life of 91.8 hours [177].

The consumption of fruits and vegetables rich in phenolic compounds may reduce risks of many civilization diseases [179]. Although there is no record of toxicity on the consumption of apigenin in food [150,180], The potential deleterious impacts of phenolic compounds utilization as a result of pro-oxidant and estrogenic activities, cancerogenic potential, cytotoxic effects, apoptosis induction and flavonoid-drug interaction [179] may likely depend on the dose being ingested.

General Considerations on Apigenin

Although there are no human clinical trials for the evaluation of the biological activities of apigenin, this flavone showed low toxicity and adverse effects [117,181,182]. In respect of interaction with other drugs, apigenin is a potent inhibitor of CYP2C9, an enzyme that is responsible for the metabolism of many drugs in the body [155,182]. Studies have demonstrated an increase in plasma levels of imatinib and venlafaxine when administered concurrently with apigenin [183,184]. Animal reproduction studies have not been conducted with apigenin [185]. Although, apigenin showed great potential in the treatment of cardiovascular diseases, inflammation, cancer, among others [181], there are needs for further studies to determine its recommended intake as a drug, in chamomile or other diet.

CONCLUSION

The current review attempt to draw attention to some key issues related to the economic values of *M. chamomilla* that are rarely reported and largely overlooked in botanical debate. The need for a comprehensive report on this multipurpose and globally available species is long overdue. The economic value of plant products could be measure in terms of quality and quantity of its active principles. The quantity of apigenin present in the plant could be used as biomarker in the industrial standardization and profiling of *M. chamomilla*. For the purpose of quality assurance, mitigation of adulteration, and pharmacognostic profiling of raw materials, semi-finished and finished products derived from *M. chamomilla*, apigenin could be useful in the regulations of the products. The easy cultivation of this species implies that its domestication could provide for local household economies. The value chains for herbal medical products have some unique characteristics, which seem to have had little impact on the discussion about value chains in the socioeconomic and developmental politics literature.

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