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18

General Introduction on Family Asteracea

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1. Introduction

Asteraceae is the largest family of the plant kingdom, very abundant and also a diverse one. The Asteraceae plants are the most widely distributed of all the families (Porter, C.L. (1969); Evans W. (1989); Hutchinson, J.(1973); Core, E. L. (1955) of the angiosperms. It includes about 1400 genera and over 25000 species (Harborne , J. B., Turner, B.L. (1984); Aboul Ela, M. A.,(1991), forming approximately 10% of the flowering plants.

Asteraceae has characteristic taxonomical characters (Muschler, R. (1912). Members of the family are generally herbs of annul or perennial habits and some tropical forms occur as shrubs. Flowers are grouped in heads known as capitula, surrounded by involucres. It is of two kinds of florets; tubular or disc florets with tubular corolla and mostly hermaphrodite, and ligulate or ray floret, with starp like corolla and mostly female.

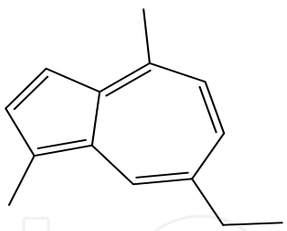
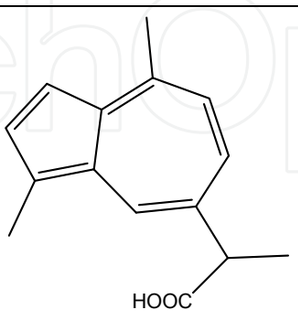
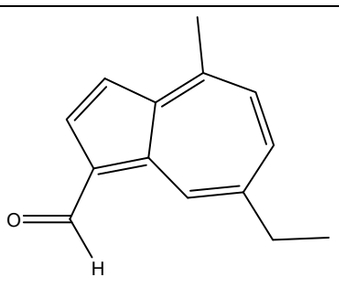
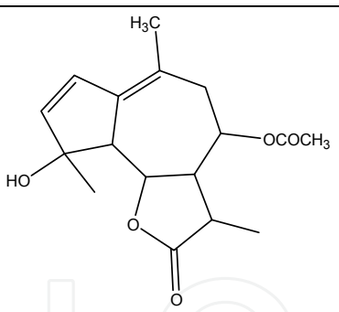
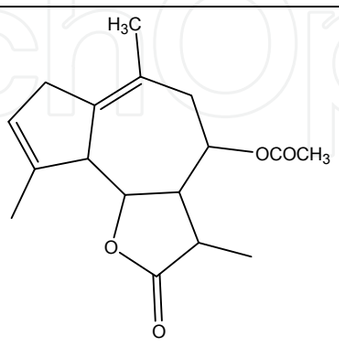
2. Chemistry of genus Matricaria

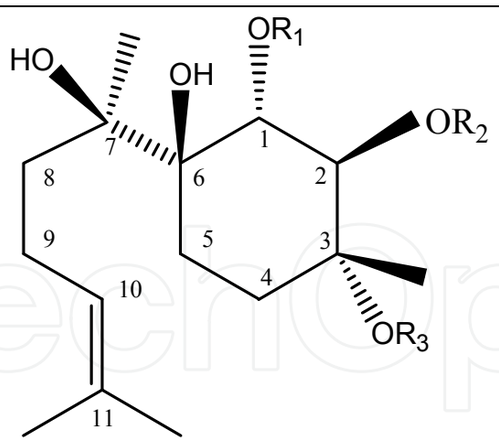
Genus Matricaria comprises plants with various secondary metabolites of different chemical nature recorded mainly in *Matricaria chamomilla*.German chamomile flowers contain 0.24- to 2% volatile oil which is blue in color. Chamomile also contains up to 8% flavone glycosides and flavonol; up to 10 percent mucilage polysaccharides; up to 0.3 percent choline; and approximately 0.1 percent coumarines. The tannin level in chamomile is less than one percent. (Alternative Medicine Review (2008))

Following is a review of the chemical compounds that have been isolated previously from genus Matricaria (Tables 1, 2, 3, and 4).

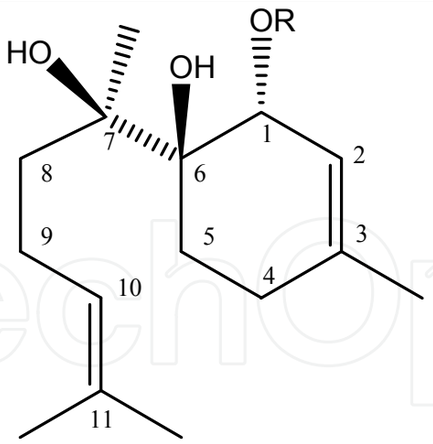
2.1 Volatile oil

Name	Source	Structure	References
a) Azulene derivatives			

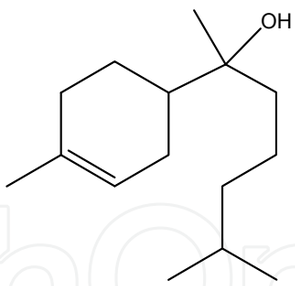
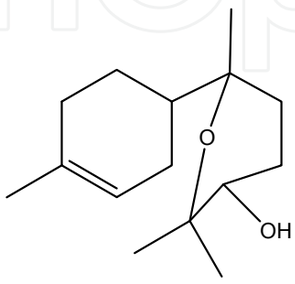
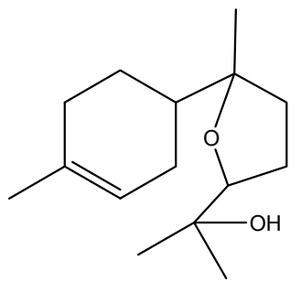
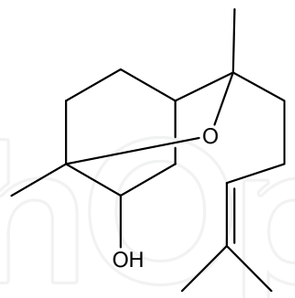
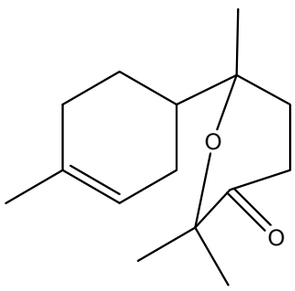
Chamazulene	*M. chamomilla*		Alternative Medicine Review 2008, Ness, A.,Metzger, J. W., Shmidt, P. C. (1996)
Chamazulene Carboxylic acid	*M. chamomilla*		Stahl, E. (1954)
Chamavioline	*M. chamomilla*		Motl, O. ,Repcak, M. (1979), Motl, O. ,Repcak, M. ,Ubik, K. (1983)
Matricin (proazulene)	Ligulate and tubular floret only of *M. chamomilla*		Alternative Medicine Review (2008), S˘orm, F.,Nowak, J., Herout, V.(1953), Cekan, Z., Herout, V., Sorm, F.,(1957)
Matricarin	*M. chamomilla*		Alternative Medicine Review (2008)
b) Sesquiterpenes i) Oxygenated sesquiterpenes			

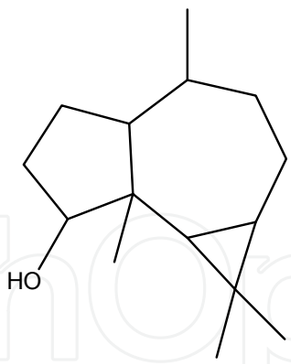
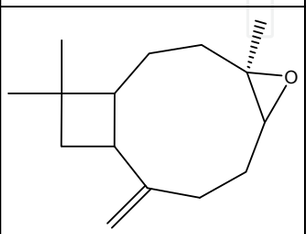
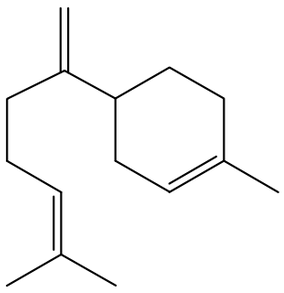
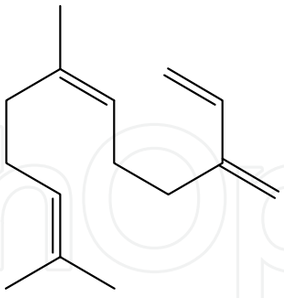
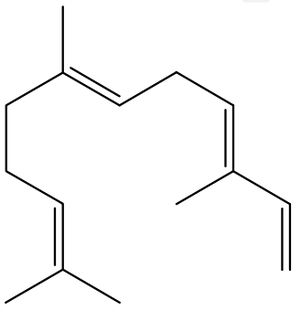


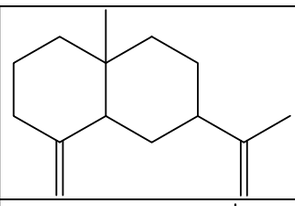
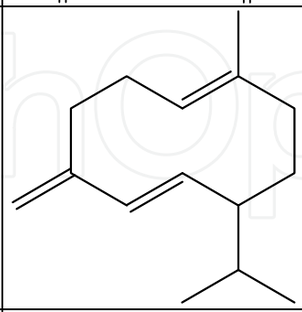
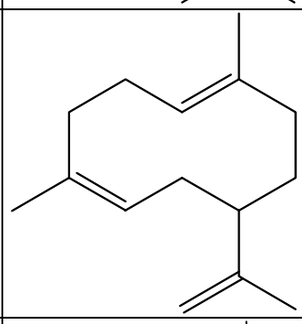
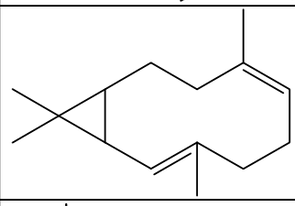
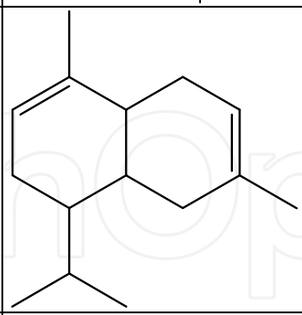
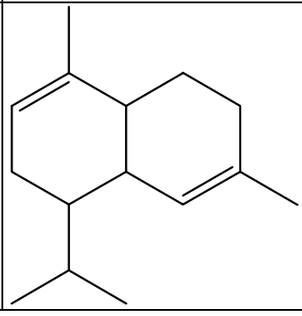
(1R*,2R*,3R*,6R*,7R*)1,2,3,6,7-pentahydroxy-bisabolol-10(11)-ene	*M. aurea*	R1	R2	R3	Ahmed A. Ahmed, Maha A. Abou Elela (1999)
		H	H	H	
(1R*,2R*,3R*,6R*,7R*)1,2,3,6,7-tetrahydroxy-1-acetoxy-bisabolol-10(11)-ene	*M. aurea*	Ac	H	H	Ahmed A. Ahmed, et al.(1993)
(1R*,2R*,3R*,6R*,7R*)1,2,3,6,7-tetrahydroxy-2-acetoxy-bisabolol-10(11)-ene	*M. aurea*	H	Ac	H	Ahmed A. Ahmed, Maha A. Abou Elela (1999)

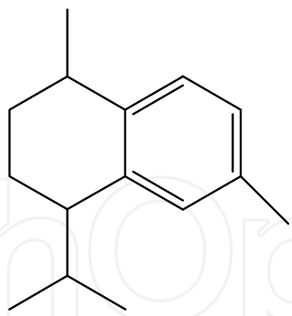
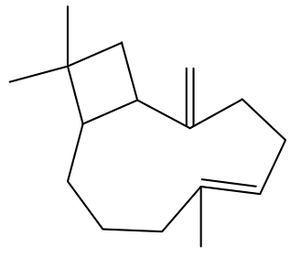
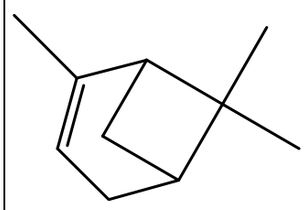
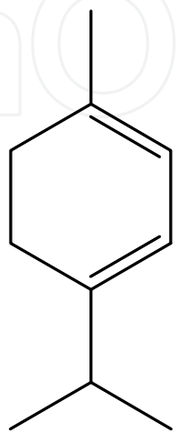


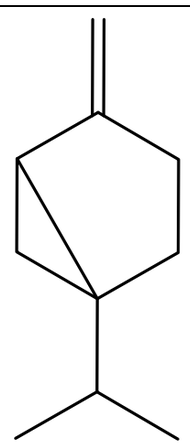
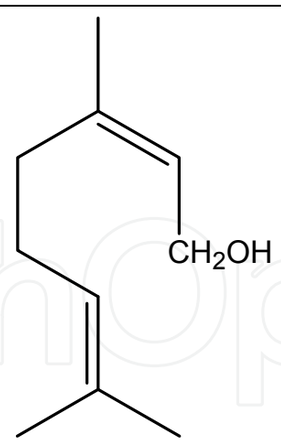
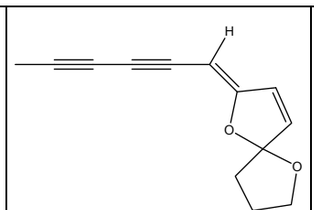
(1R*,6R*,7R*)1,6,7-trihydroxy-bisabolol-2,10- diene	*M. aurea*	R	Ahmed A. Ahmed, et al.(1993)
		H	
(1R*,6R*,7R*)1,6,7-trihydroxy-1-acetoxybisabolol-2,10-diene	*M. aurea*	Ac	Ahmed A. Ahmed, et al.(1993)

(-)-α-bisabolol	*M. chamomilla*		Alternative Medicine Review (2008), Sˇorm, F.,Zaoral M.,Herout, V.(1951)
(-)-α-bisabolol oxide A	*M. chamomilla*		Alternative Medicine Review 2008, Sampath , V., et al (1969)
(-)-α-bisabolol oxide B	*M. chamomilla*		Alternative Medicine Review (2008), Sampath ,V.,Sabata, et al ,(1969)
(-)-α-bisabolol oxide C	*M. chamomilla*		Schilcher, H., et al (1976)
α-bisabolone oxide	*M. chamomilla* growing in turkey		Hölzl, J., Demuth, G.(1973)

Spathulenol	*M. chamomilla*		Alternative Medicine Review (2008), Motl, O., et al(1977)
Caryophyllene epoxide	*M. chamomilla*		Reichling, J., et al (1983)
ii) Unsaturated sesquiterpenes			
β-bisabolene	*M. chamomilla*		Anne ORAV, Tiiu KAILAS, and Kaire IVASK (2001)
Trans-β- farnesene	*M. chamomilla*		Alternative Medicine Review (2008), Lemberovics, E. (1979)
Trans -α-farnesene	*M. chamomilla*		Lemberovics, E. (1979)

β-selinene	*M. chamomilla*		A.Pizard, et al.(2006)
Germacrene D	*M. chamomilla*		Anne ORAV, Tiiu KAILAS, and Kaire IVASK (2001) A.Pizard, et al.(2006)
Germacrene A	*M. chamomilla*		A.Pizard, et al.(2006)
Bicyclo germacrene	*M. chamomilla*		A.Pizard, et al.(2006)
Cadinene	*M. chamomilla*		Alternative Medicine Review (2008), Anne ORAV, Tiiu KAILAS, and Kaire IVASK (2001)
α-muurolene,	*M. chamomilla*		Motl, O., Repcak, M.(1979)

Calamemene	*M. chamomilla*		Motl, O., Repcak, M.(1979)
β-caryophyllene	In the root oil of *M. chamomilla*		Reichling, J., et al (1983)
c) Monoterpenes			
α-pinene	*M. chamomilla*		Anne ORAV, Tiiu KAILAS, and Kaire IVASK (2001), A.Pizard, et al.(2006)
α-Terpinene	*M. chamomilla*		A.Pizard, et al.(2006)

Myrcene	*M. chamomilla*		Stransky, K., et al., (1981)
Sabinene	*M. chamomilla*		Anne ORAV, Tiiu KAILAS, and Kaire IVASK (2001) , A. Pizard, et al.(2006)
Gerianol	*M. chamomilla*		Stransky, K., et al., (1981)
Spiroethers			
Cis (Z)-enyne dicycloether *cis*-2-[hexadiyne)- (2,4)-ylidene]-1,6-dioxaspiro-[4,4]-nonene)	*M. chamomilla*		Alternative Medicine Review (2008), Bohlmann, F., Zdero, C. (1982), Bohlmann, F., et al ,(1961)

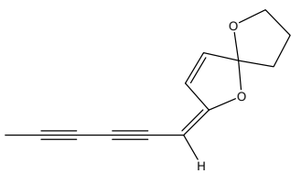
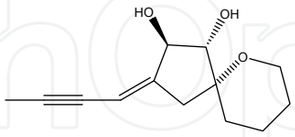
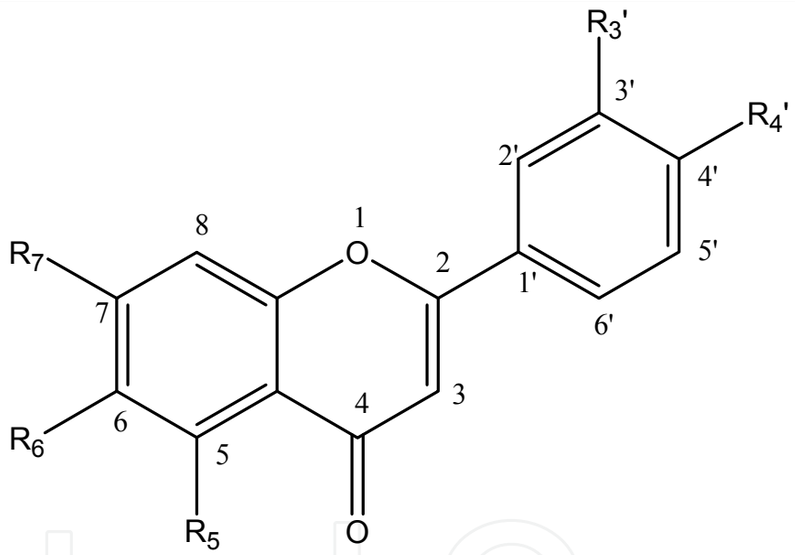
Trans (E)-enyne dicycloether *trans*-2-[hexadiyne)-(2,4)-ylidene]-1,6-dioxaspiro-[4,4]-nonene	*M. chamomilla*		Alternative Medicine Review (2008), Bohlmann, F., et al ,(1961), Bohlmann, F., Zdero, C. (1982)
(3S*,4S*,5R*)-(E)-3,4-dihydroxy-2-(hexa-2,4-diynyliden)-1,6-dioxaspiro-(4,5) decane	*M. aurea*		Ahmed A. Ahmed, Maha A. Abou Elela (1999)

Table 1. Volatile components isolated from Matricaria species

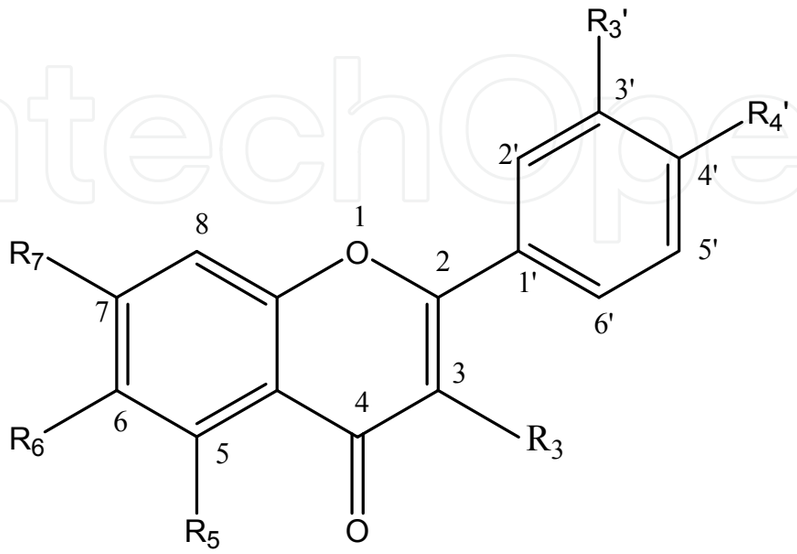
2.2 Flavonoids

a) Flavone aglycon and glycosides isolated from species *Chamomilla*



Name	Source	R_5	R_6	R_7	$R_{3'}$	$R_{4'}$	Ref.
i) Flavone aglycon							
Apigenin	Ligulate florets flowers	OH		OH		OH	Powe, F., Browning, H. Jr. (1914), S˘orm, P.,et al.,(1952), Kunde, R., Isaac, O.(1979), Carle, R. and Isaac, O. (1985)
Luteolin	flowers	OH		OH	OH	OH	Kunde, R., Isaac, O.(1979), Carle, R. and Isaac, O. (1985)
Chrysoseriol	flowers	OH		OH	OCH_3	OH	Carle, R. and Isaac, O. (1985) , Reichling, J., et al., (1979)

ii) Flavone glycosides							
Luteolin-7-glucoside	Egyptian chamomile floret (leaves) Ligulate florets	OH		OGlu	OH	OH	Kunde, R., Isaac, O.(1979), Elkiey, M. A.,et al., (1963), Greger, H. (1975)
Luteolin-4′-glucoside		OH		OH	OH	OGlu	
Chrysoseriol-7-glucoside	Leaves	OH		OGlu	OCH_3	OH	Greger, H. (1975)
Apigenin-7-glucoside (Apigetrin)	Ligulate floret	OH		OGlu		OH	Kunde, R., Isaac, O.(1979), Lang, W., Schwandt, K. (1957), Hörhammer, L., Wagner, H., Salfner, B. (1963)
Apigenin-7-(6′′-O-acetyl)-glucoside	Ligulate florets	OH		OGlu-ac.		OH	Kunde, R., Isaac, O.(1979), Redaelli, C., Formentini, L., Santaniello, E. (1979)
Apigenin-7-(6′′-O-apiosyl)-glucoside (apiin)	Ligulate florets	OH		OGlu-Apio.		OH	Kunde, R., Isaac, O.(1979), Wagner, H., Kirmayer, W. (1957)
b) Flavonol aglycones and glycosides isolated from *Chamomilla* species							



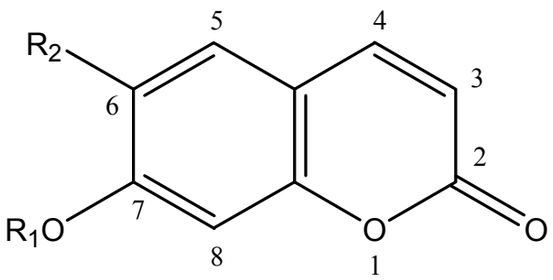
Name	Source	R_3	R_5	R_6	R_7	$R_{3'}$	$R_{4'}$	Ref.
i) Flavonol aglycones								
Lutuletin	Tubular floret flowes	OH	OH	OCH_3	OH	OH	OH	Kunde, R., Isaac, O.(1979), Carle, R. and Isaac, O. (1985) , Ahmed A. Ahmed, Maha A. Abou Elela (1999)
Quercetin	Leaves Tubular floret flowers	OH	OH		OH	OH	OH	Kunde, R., Isaac, O.(1979), Carle, R. and Isaac, O. (1985), Greger, H. (1975)
Chrysosplenol	Chamomile flower	OCH_3	OH	OCH_3	OCH_3	OH	OH	Carle, R. and Isaac, O. (1985), Exner, J., et al., (1981), Hänsel, R., Rimpler, H., Walther, K. (1966)
Chrysosplenitin	Flowers	OCH_3	OH	OCH_3	OCH_3	OCH_3	OH	Carle, R. and Isaac, O. (1985) , Hänsel, R., Rimpler, H., Walther, K. (1966)
Eupatoletin	Chamomile flower Ligulate florets	OH	OH	OCH_3	OCH_3	OH	OH	Kunde, R., Isaac, O.(1979), Carle, R. and Isaac, O. (1985), Exner, J., et al., (1981), Hänsel, R., Rimpler, H., Walther, K. (1966)
Eupalitin	Chamomile flower	OH	OH	OCH_3	OCH_3		OH	Carle, R. and Isaac, O. (1985), Exner, J., et al., (1981), Hänsel, R., Rimpler, H., Walther, K. (1966)
ii) Flavonol glycosides								
Quercetin-7-glucoside (Quercimeritrin)	Tubular floret	OH	OH		OGlu	OH	OH	Kunde, R., Isaac, O.(1979), Lang, W., Schwandt, K. (1957) , Horhammer, L.,

								Wagner, H., Salfner, B. (1963)
Quercetin-3-rutinoside	Chamomile flower	OGlu-Rham	OH		OH	OH	OH	Elkiey, M. A.,et al., (1963)
Quercetin-3-galactoside	Chamomile flower	OGal	OH		OH	OH	OH	Elkiey, M. A.,et al., (1963)

Table 2. Flavone and flavonol aglycon and glycosides isolated from species *Chamomilla*

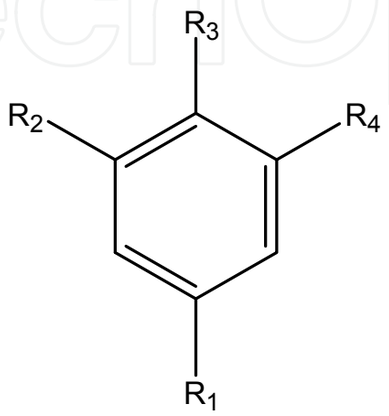
2.3 Coumarines and other polyphenolic compounds

a) Coumarines



Name	Source	R_1	R_2	Ref.
Herniarin	Ligulate and Tubular floret of *M. chamomilla*	CH_3	H	Schilcher, H. (1985)
Umbelliferone	Ligulate and Tubular floret of *M. chamomilla*	H	H	Schilcher, H. (1985)
Isoscopoletin	*M. chamomilla*	CH_3	H	Kotov, A. G., et al., (1991)
Esculetin	*M. chamomilla*	H	OH	Kotov, A. G., et al., (1991)
Scopoletin	*M. chamomilla*	H	OCH_3	Kotov, A. G., et al., (1991)

b) Phenyl carboxylic acid



Name	Source	R_1	R_2	R_3	R_4	Ref.
Synergic acid	Ligulate and tubular floret of *M. chamomilla*	COOH	OCH_3	OH	OCH_3	Reichling, J., et al., (1979)
Vanillic acid	Ligulate and tubular floret of *M. chamomilla*	COOH	H	OH	OCH_3	Reichling, J., et al., (1979)
Anisic acid	*M. chamomilla*	COOH	H	OCH_3	H	Reichling, J., et al., (1979)
Caffeic acid	*M. chamomilla*	$CH_2{=}CH_2COOH$	OH	OH	H	Reichling, J., et al., (1979)

Table 3. Coumarines and other polyphenolic compounds isolated from genus Matricaria

2.4 Miscellaneous substances

Chamomile contains up to 10% mucilage polysaccharides (Alternative Medicine Review (2008)).The main chain of the polysaccharide consists of α-1-> 4 connected D-galacturone acids (Carle, R. and Isaac, O.,(1985)). In addition to xylose, arabinose, galactose, glucose, rhamnnose (Janecke, H., Weiser, W. (1964))(Janecke, H., Weiser, W.(1965)).

Recently, three polysaccharides were isolated and showed remarkable antiphlogistic activity against mouse ear edema induced by crotone oil (Füller, E., (1992)) as fructane (74.3% fructose and 3.4% glucose, similar to inulin), rhamnogalacturonane (28% uronic acid, 3.2% protein, similar to pectin), and arabino-3, 6-galactane glycoproteins.

- Chamomile contains up to 0.3% choline ((Alternative Medicine Review (2008)), (Bayer, J. et al. (1958)) which is supposed to be participating in the antiphlogistic activity of the extract.
- More than 13 amino acids were detected (Schilcher, H.,(1980)) from the fresh chamomilla herb as L-leucine, DL-methionine, DL-α-alanine, glycine, L-histidine, L-(+)-lysine, DL- threonine, DL-serine, and L-glutaminic acid.
- Tannin level is less than 1% (Alternative Medicine Review (2008).

3. Some reported pharmacological activity of the chemical constituents of Matricaria

Several pharmacological actions have been assigned for German chamomile, based primarily on *in vitro* and animal studies. Such actions include antibacterial, antifungal, anti-inflammatory, antispasmodic, anti-ulcer, antiviral, carminative, and sedative effects (Alternative Medicine Review 2008). It is important to mention that therapeutic effectiveness is mainly due to the combined pharmacological and biochemical effects of several chamomile constituents (Schilcher, H.,(1987)).

3.1 Apoptotic effect against cancerous cell

- Darra et al. in 2008 showed that α-bisabolol is able to rapidly, efficiently and selectively induce apoptosis in malignant tumor cells by targeting lipid rafts on cell membranes. Thereafter, α-bisabolol could interact with Bid protein (one of pro-apoptotic Bcl-2 family proteins, analyzed either by Surface Plasmon Resonance method or by intrinsic fluorescence measurement) recruited in lipid rafts region after α-bisabolol treatment, which may be involved in the transduction pathway from plasma membranes to intracellular compartments including mitochondria. However, toxicity towards normal cells or in animals was absent. (Elena Darra, et al., (2008))
- In 2007, Farnesol had been demonstrated by Joo et al. to inhibit proliferation and induce apoptosis in a number of neoplastic cell lines from different origins (J.H. Joo,et al., (2007)) with preferential action in transformed cells versus untransformed cells (Adany, Cancer Lett. (2000)) and (Srivastava JK, Gupta S. (2007))
- Other preliminary study by Srivastava et al. in 2007 recorded that *in vitro* exposure to chamomile results in differential apoptosis in cancerous cells but not in normal cells at similar doses; apigenin and apigenin glycosides appear to be the key components responsible for these effects, (Deendayal patel et al. (2007))
- Moreover, Patel *et al in 2007* identified many mechanisms of action for apigenin-mediated cancer prevention and therapy, including estrogenic/anti-estrogenic activity, anti-proliferative activity, induction of cell-cycle arrest and apoptosis, prevention of oxidation, induction of detoxification enzymes, regulation of the host immune system, and changes in cellular signaling. This suggests that apigenin possesses enormous potential for development as a promising cancer chemopreventive agent in the near future for breast, cervical, colon, lung, prostate, ovarian, skin, endometrial, thyroid, and gastric, hepatocellular, and adrenocortical cancers as well as leukemia. Pre-clinical studies of various animal models of cancer that closely simulate human cancers are still needed (Barton, H. 1959).

3.2 Sedative and anxiolytic effect

- Shinomiya et al. (Kazuaki S. et al., (2005)) investigated the hypnotic activities of chamomile and passiflora extracts using sleep-disturbed model rats. A significant decrease in sleep latency was observed with chamomile extract at a dose of 300 mg/kg. His findings strongly suggested that chamomile is a herbal product possessed both hypnotic and anxiolytic activity in animals.
- (Avallone R.,et al., (2000) showed that apigenin, a flavonoid isolated from *Matricaria chamomilla*, significantly reduced the locomotor activity in the open field test of rats.
- (Viola H., et al.,(1995) , in a study about intraperitoneal administration of chamomile extract in mice, concluded that apigenin functions as a ligand for benzodiazepine receptors, resulting in anxiolytic and mild sedative effects, but no muscle relaxant or anticonvulsant effects. He also reported that apigenin extracted from chamomile flowers inhibited [3H]-flunitrazepam binding in the bovine cerebral cortex.
- Gould L., et al.,(1973) reported that hospitalized patients were given a strong chamomile tea, and ten of the twelve patients immediately fell into a deep sleep lasting 90 minutes.
- Della Loggia, R., et al.,(1981)) also demonstrated that chamomile extract caused a significant prolongation of sleeping time induced by barbiturates in mice.

3.3 Antispasmodic effect

Both flavonoids and essential oil contribute to the musculotropic antispasmodic effect of chamomile. Apigenin, alpha-bisabolol, and the cis-spiroethers appear to provide the most significant antispasmodic effects. (Alternative Medicine Review (2008).

- Maschi *et al.* in 2008 reported the spasmolytic activity of chamomile was through inhibition of cAMP-PDE for the first time. Human platelet cAMP-PDE and recombinant PDE5A1 were assayed in the presence of chamomile infusions. Chamomile inhibited cAMP-PDE activity (IC50) 17.9-40.5 μg/mL), while cGMP-PDE5 was less affected (-15% at 50 μg/mL). Among the individual compounds tested, flavonoids showed an inhibitory effect (IC50) 1.3-14.9 μM), contributing to around 39% of the infusion inhibition.
- Carle, R., Gomaa, K. in 1992 demonstrated that the chamomile oil itself, (-)-α- bisabolol, the bisabolol oxides A and B, and the enyne dicycloethers have a papaverine-like musculotropic spasmolytic activity. In addition, the coumarin derivates umbelliferone and herniarin are also antispasmodically active,(Acheterrath-Tuckermann,et al., 1980)
- In Tests that was performed using rat or rabbit duodenum, where the contractions were induced by barium chloride, acetyl choline, and histamine (Hava M., Janku J. (1957), (Janku, J. (1981), apigenin inhibits the contractions of smooth muscle and those of seminal vesicle of cavy and of rabbit uterus. 10 mg of apigenin were equieffective to about 1 mg of papaverine as for musculotropic effect. (Della Loggia, R. 1985)
- Other flavonoids contribute to the smooth muscle relaxation but to lesser degree. They can be classified in descending activity as follows: apigenin, quercetin, luteolin, kaempferol, luteolin-7-glucoside, and apigenin-7-glucoside. (Hörhammer, L.,et al., (1963)

3.4 Antimicrobial effect

Preliminary *in vitro* studies on the antimicrobial activity of chamomile have yielded promising results.

- Annuk H,et al., in 1999 proved that chamomile extract at concentration 2.5 mg/ml killed trichomonads effectively. It also blocked aggregation of various strains of *Escherichia coli*.
- Shikov, A., et al., in 1999 demonstrated that chamomile oil extract inhibited the production of urease at *H. pylori*. It was suggested that the mechanism of therapeutic action of chamomile oil is based on inhibition of colony activity of *H. pylori* and an inhibiting effect on adhesion of this microorganism of phospholipid — lecithin.
- Turi M. *et al.* in 1997 showed that chamomile extract inhibited the growth of poliovirus and herpes virus while chamomile esters and lactones demonstrated activity against *Mycobacterium tuberculosis* and *Mycobacterium avium*.
- Berry M. in 1995 showed that chamomile oil, at a concentration of 25 mg/mL, demonstrated antibacterial activity against such Gram-positive bacteria as *Bacillus subtilis*, *Staphylococcus aureus*, *Streptococcus mutans*, and *Streptococcus salivarius*, as well as some fungicidal activity against *Candida albicans*
- The strongest antibacterial activity was recorded for α- bisabolol. It is active in low concentrations against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli,*

Streptococcus faecalis, and *Pseudomonas aeruginosa* and inhibits the growth of strains of *Bacterium phlei* that were resistant against standard anti-infectives (Szabo-Szalontai, M., et al., (1976) and (Szalontai, M.,et al., (1975). Bisabolol, together with enyne dicycloethers, also showed fungistatic activity against *Candida albicans, Trichophytone menthagrophytes,* and *Trichophytone rubrum* at a concentration of 100µg/ml. Chamazulene also had this fungistatic activity, but at higher concentrations (Szalontai.,M., Verzar-petri, G., Florian, E. (1977).

3.5 Anti inflammatory effect

- Recent study in 2009 by Srivastava *et al.* done on aqueous extract of chamomile flowers growing in Egypt, where LPS-activated RAW 264.7 macrophages were used as in vitro model, Chamomile treatment inhibited the release of LPS-induced PGE2 in RAW 264.7 macrophages. This effect was found to be due to inhibition of COX-2 enzyme activity by chamomile. In addition, chamomile extract caused reduction in LPS-induced COX-2 mRNA and protein expression, without affecting COX-1 expression. This suggested that mechanism of action of chamomile on the inhibition of PGE2 production was due to the suppression of the COX-2 gene expression and direct inhibition of COX-2 enzyme activity which is similar to non-steroidal anti inflammatory drugs.
- (-)-α- bisabolol was capable of inhibiting both 5-lipoxygenas and cyclooxygenase (Szelenyi J., Isaac, O., Thiemer, K., (1979)). It has antipyretic activity against yeast-induced pyrexia of the rat (Büchi, O. (1959)). Other experiments showed that (-)-α-bisabolol was capable of inhibiting the formation of ulcers induced by indomethacin, stress, or alcohol (Szelenyi J., Isaac, O., Thiemer, K., (1979))
- Regarding azulenes, their anti inflammatory effect was proven (Zierz, P., Kiessling, W (1953), (Zierz, P., et al. (1957) through inhibition of histamine liberation, inhibition of 5-hydroxytryptamine liberation, anti-hyaluronidase effect, and a decrease of the capillary activity (Uda, T.(1960). This is besides to the activation of the ACTH production (Kato, et al. (1959).
- Chamazulene was identified as the antiphlogistic principle of chamomile oil in a test system of chemosis caused by mustard oil in rabbit and cavy eye (Heubner, et al. (1933) and Pommer (1942)). It was proved by Ammon et al. in 1996 to inhibit 5-lipoxygenase.
- Antiphlogistic activity of flavonoids was proved much later (Baumann, J., et al., (1980)), (Carle, R., Gomaa, K. (1992), (Della loggia, R. (1985)), Della loggia, R., et al., (1984)), (Della loggia R., et al., (1986), Wurm, G., (1982). Apigenin even exceeded the activity of indomethacin and phenylbutazone. The experiments further showed that apigenin had both a positive influence on the vascular phase of the inflammation (e.g., edema) and on the cellular phase (e.g., the migration of leucocytes). Antiphlogistic activity of flavonoids decreased in the following order: Apigenin > luteolin > quercetin > myricetin > apigenin-7-glucoside > rutin.

3.6 Anti ulcerative effect

Torrado S, et al., in 1995 reported that significant protective effect against gastric toxicity of 200 mg/kg acetylsalicylic acid where achieved after oral administration of chamomile oil to rats at doses ranging from 0.8-80 mg/kg bisabolol. Moreover, *in vitro* studies revealed that alpha-bisabolol inhibited gastric ulcer formation induced by indomethacin, ethanol, or stress, Szelneyi I, Isaac O., thiemer K. (1979)

3.7 Other Pharmacological actions

3.7.1 Inhibition of Aflatoxin G1 production

Yoshinari et al. in 2008 showed that the spiroethers of German chamomile inhibited production of aflatoxin G1 AFG1 by *Aspergillus parasiticus* with inhibitory concentration 50% (IC50) values of 2.8 and 20.8 mM respectively. This is through inhibiton of cytochrome P450 monooxygenase CYPA and without inhibiting fungal growth. In addition, it also inhibited production of 3-acetyldeoxynivalenol 3-ADON by *Fusarium graminearum* by inhibiting TRI4. The inhibitory activity of the (E)-spiroether isomer was much stronger than that of the (Z)-spiroether in both cases. Inhibition of TRI4 by the spiroethers showed that TRI4 may be a good target for inhibiting biosynthesis of trichothecene mycotoxins.

3.7.2 Protective effect on diabetic complications

- Kato et al. in 2008 investigated the effects of chamomile hot water extract and its major components on the prevention of hyperglycemia and the protection or improvement of diabetic complications in diabetes mellitus. Results suggested that a suppressive effect of chamomile on blood glucose level was independent of the inhibition of intestinal α-glycosidases but depended on the inhibition of hepatic glycogen phosphorylase (GP). Furthermore, chamomile extract has good inhibitory potency against aldose reductase (ALR2), which plays key roles in the polyol pathway and its activation promotes the progress of diabetic complications. Chamomile components, umbelliferone, esculetin, luteolin, and quercetin, could inhibit sorbitol accumulation in human erythrocytes. Therefore, daily consumption of chamomile tea with meals could be potentially useful in the prevention and self-medication of hyperglycemia and diabetic complications. ATSUSHI KATO,et al ., (2008)

3.7.3 Antioxidant effect

- Lado *et al.* in 2004 studied the volatile oil of several plants and their main components to determine their antioxidant activity. This was done by using the modified method of ferric reducing ability of plasma (FRAP). The reducing ability of juniper, yarrow, and chamomile (145.107 ± 0.007mmol/kg) was very significant and it was twice as high as the average values of the other plants (Lavander, salvia, rosemary, etc). The reducing abilities of the components of volatile oils are lower than those of volatile oils; therefore, the reducing capacities of volatile oils not only attributed solely to terpenes, but also other biologically active compounds may also contribute to ferric reduction and in electron scavenging (Cristina Lado, et al.,(2004)).

3.7.4 Inhibition of morphine dependence

- Gomaa *et al.* in 2003 showed that co-administration of *M. chamomilla* extract containing 0.3% apigenin with morphine not only inhibited dependence to morphine but also prevented the increase in plasma cAMP induced by naloxone-precipitated abstinence. Furthermore, naloxone precipitated morphine withdrawal behavior syndrome was abolished by acute *M. chamomilla* treatment before naloxone challenge, indicating that *M. chamomilla* extract has an inhibitory effect on the expression of naloxone-precipitated morphine withdrawal syndrome.

3.7.5 Tachykinin receptor antagonist

- Yamamoto et al. in 2002 discovered a novel and potent nonpeptide tachykinin NK1 receptor antagonist in the extract of dried flowers of *Matricaria chamomilla.* . It has a unique structure of a polyacylated Spermine which was established as *N*1, *N5, N10, N14*-tetrakis [3-(4-hydroxyphenyl)-2-propenoyl]-1, 5, 10, 14-tetraazatetradecane (tetracoumaroyl spermine). The *K*i values of 1a, estimated from the inhibitory action on the substance P (SP)-induced contraction of the guinea pig ileum and the inhibition of the binding of [3H][Sar9, Met(O2)11]SP to human NK1 receptors, were 21.9 nM and 3.3 nM, respectively.

4. Clinical indications of *Matricaria chamomilla*

German chamomile is a well-known and widely used herb in different parts of the world. Few well designed, randomized, double-blind; placebo-controlled studies are available to fully assess its therapeutic benefit. (Alternative Medicine Review 2008)

4.1 Gastrointestinal effect

- De la Motte S, (1997) conducted a prospective, randomized, multicenter, double-blind, parallel group trial, where 79 children (ages six months to five years) with acute, non complicated diarrhea received either a commercial preparation of apple pectin and chamomile extract or placebo for three days, in addition to a typical rehydration and re-alimentation diet. At the end of three days, significantly more children in the pectin/chamomile group (85%) experienced diarrhea alleviation compared to the placebo group (58%) ($p<0.05$). The pectin/chamomile combination experienced a significant 5.2-hour shorter duration of symptoms compared to the placebo group. Weizman Z. et al. in 1993 in double-blind studies observed the efficacy of a herbal decoction consisting of German chamomile, vervain, licorice, fennel, and balm mint on 68 healthy infants with colic. For seven days the infants (ages 2-8 weeks) received 150 mL of the herbal preparation or placebo with each colic episode, but no more than three times daily. After seven days, 57 percent of the infants receiving the herbal preparation experienced colic relief compared to 26 percent in the placebo group ($p<0.01$).
- Schmid et al. in 1975 showed that chamomile extract is successfully applied in pediatrics due to its carminative and spasmolytic effect with diseases of the gastrointestinal tract and the effect as such is said to set in immediately after taking the preparation. The internal administration of chamomile tea or preparations from chamomile extracts is appropriate in different gastric troubles that can be classed under term of "dyspepsia," as recorded by Weiss in 1987.

4.2 General anti-inflammatory effect

- In 1999 Schilcher demonstrated that chamomile extract therapy is advisable in pediatrics for sensitive skin care of babies, treatment of an inflamed skin or skin defects (as dermatitis ammoniacalis, scald and burn areas and exfoliative dermatitis), and for the treatment of inflammations of the nose and the paranasal sinus by application of a chamomile bath and inhalation.
- Nasemann et al. in 1991 reported about the antiphlogistic effect of Kamillosan® ointment in comparison with a nonsteroidal ointment in case of episiotomies, with

colpitis senilis, and about the improvement of the healing of wounds after surgical operations carried out by laser in gynecology after taking a chamomile (hip) bath.
- Carle et al. in 1987, and according to reports of various gynecological hospitals, showed that chamomile extract is a suitable remedy for the treatment of bartholinitis, vulvitis, and mastitis and in rare cases secondarily healing episiotomies.

4.3 Dermatologyical effect

- Stechele in 1991 and according to a pediatrician's open report showed that very good results could be achieved by using chamomile ointment for the treatment of napkin dermatitis.
- Aertgeerts P et al. in 1985, in an open, bilateral comparative trial, 161 patients with eczema on their hands, forearms, and lower legs initially treated with 0.1-percent diflucortolone valerate received one of four treatments: chamomile cream (Kamillosan), 0.25-percent hydrocortisone, 0.75-percent fluocortin butyl ester (a glucocorticoid), or 5.0-percent bufexamac (a nonsteroidal anti-inflammatory). After 3-4 weeks, the chamomile cream was found to be as effective as hydrocortisone and demonstrated superior activity to bufexamac and fluocortin butyl ester.
- As for Born in 1991, chamomile extract was applied for the irrigation of undermined margins of a wound, pouches, sinus tracts, and hip baths, correspondingly diluted or in concentrated form for swabbing inflammatory lesions of the mucosa.
- Contzen in 1975 proved that the chamomile bath can be used successfully with the local treatment of deep second-degree burns. Apart from an accelerated cleansing process of a wound a significant improvement of the granulation is also observed. Deep necroses are excised; superficial ones heal without proteolytic ferments.
- Glowania HJ et al. in 1987and through a double-blind trial examined the therapeutic efficacy of a topical chamomile extract on 14 patients with weeping dermabrasions from tattoo applications. Those using chamomile noted a statistically significant decrease in the weeping wound area and increased drying compared to the placebo group.

4.4 Sleep enhancement

In an open case study to examine the cardiac effects of two cups of chamomile tea on patients undergoing cardiac catheterization, Gould L. et al. observed that 10 of 12 patients in the study achieved deep sleep within 10 minutes of drinking the tea, Gould L, et al. (1973). The patients had a small but significant increase in mean brachial artery pressure. No other significant hemodynamic changes were observed.

4.5 Radiation therapy

- Fidler P. et al. in 1996 conducted a randomized, double-blind study with 164 cancer patients taking 5-fluorouracil (5-FU) chemotherapy. The patients rinsed three times daily with either a chamomile mouthwash or placebo. After 14 days, no difference was observed between the two groups in the incidence of stomatitis induced by 5-FU.
- Carl W. et al. 1991 examined the effect of 15 drops of Kamillosan Liquidum, a German chamomile mouthwash preparation, in 100 mL of water taken three times daily, for radiation and/or chemotherapy-induced mucositis (characterized by inflammation and ulceration of the gastrointestinal tract including the mouth). Cancer patients (n=98)

were divided into two groups. One group of 66 patients (20 undergoing radiation therapies, 46 undergoing chemotherapy) participated in prophylactic oral care with the mouthwash. The remaining 32 patients underwent chemotherapy and were treated therapeutically after mucositis had developed. Of the 20 patients undergoing radiation, only one developed high-grade (grade 3) mucositis in the final week of treatment, 65 percent developed intermediate grade mucositis, and 30 percent developed low-grade mucositis. Of the 46 patients concurrently receiving chemotherapy and the mouthwash, 36 remained free of any clinically significant mucositis. Of the 32 patients with existing mucositis, all noted immediate relief from mouth discomfort, and within seven days almost all patients had no clinical sign of mucositis.

- Maiche AG et al. in 1991 carried out a double-blind, randomized, placebo-controlled study, where 48 women receiving radiation therapy for breast cancer were treated topically with either chamomile cream or placebo (almond oil) to protect the radiation-treated area. While there were no significant differences between the two groups in objective scores of skin irritation, the patients preferred the chamomile containing cream to the placebo for its rapid absorption and stainlessness.
- According to Bulmenberg, E.-W., Hoefer-Janker, H. (1972), the reactions of mucosa of the rectum resulting from a highly dosed radiation therapy, frequently felt to be unendurable; can also be treated successfully with chamomile extract. For that purpose enema is given three times a week; besides antiphlogistic properties, this also has a mild cleaning effect

4.6 Other uses

- According to Hinz in 1995, a standardized ethanolic-aqueous chamomile flower extract is suitable for the adjuvant therapy of *Angina lacunaris* and for the symptomatic treatment of herpangina often occurring in (early) childhood. In addition has a pain-alleviating effect in cases of inflammatory and painful esophageal diseases.

5. Photograph of the two matricaria specie

Fig. 1. Photograph of *Matricaria aurea*

Fig. 2. Photograph of *Matricaria chamomilla.*

(10-40cm in height, with erect, branching stems **.**the capitulum (to 1.5cm in diameter) comprises 12-20 white ligulate florets surrounding a conical hollow receptacle on which numerous yellow tubular (disk) florets are inserted (Bruneton J. (1995))

6. Conclusions and recommendations

A lot of studies have been conducted on *Matricaria chamomilla* all over the world where many important biologically active compounds have been separated and identified. However, very few studies are available for *Matricaria aurea* world wide. Nowadays, researches are focusing on exploring the pharmacological profile of compounds from natural origin, where promising results aroused. Challenges remain in finding ways to benefit from these biologically important compounds in treating human health problems.

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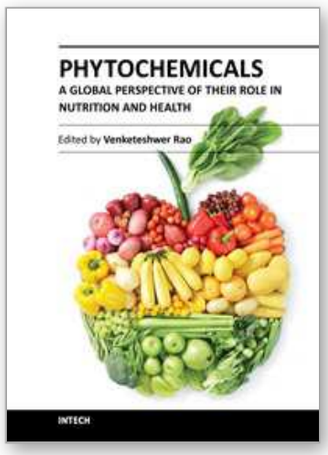

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Phytochemicals are biologically active compounds present in plants used for food and medicine. A great deal of interest has been generated recently in the isolation, characterization and biological activity of these phytochemicals. This book is in response to the need for more current and global scope of phytochemicals. It contains chapters written by internationally recognized authors. The topics covered in the book range from their occurrence, chemical and physical characteristics, analytical procedures, biological activity, safety and industrial applications. The book has been planned to meet the needs of the researchers, health professionals, government regulatory agencies and industries. This book will serve as a standard reference book in this important and fast growing area of phytochemicals, human nutrition and health.

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