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An Up-to-Date Review of Phytochemicals and Biological Activities in *Chrysanthemum* spp

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The *Chrysanthemum* is a well-known traditional Chinese medicinal herb which has been used as a drug for thousands of years. From the detailed literature survey it is determined that the dried flowers of *Chrysanthemum* contain organic groups such as alkanes, flavonoids, terpinoids, unsaturated fatty acids and polysaccharides which belongs to Secondary constituents in Phytochemicals classification. The knowledge and analysis of bioactive compounds present in the *Chrysanthemums* can be used for next generation drug development process. The developments of new drugs against diabetes and prostate cancer have become global concern. Hence the present study leads to identify the new strategies which are needed to develop multi-functional drugs against various human diseases using *Chrysanthemum* plant. Owing to antifungal, antibacterial and anti-inflammation activities, *Chrysanthemum* have much attention in the field of biomolecules research. In general Phytochemicals can be classified as primary and secondary constituents. One can understand the fascinating properties of biological compounds via phytochemical analysis which are present in the plants. Therefore, the present study gives a better understanding of phytochemical properties of *Chrysanthemum* and new foundations for the production of non-toxic and eco-friendly drugs of today and the future.

Keywords: *Chrysanthemum,* Phytochemicals, Biological activities.

Introduction of *Chrysanthemum* spp.

Chrysanthemums have a wide range of applications such as efficient drugs for various diseases in traditional medicinal field, healthy herbal tea in food processing, hardy blooms in gardening, and indoor air pollution control in environmental monitoring. In addition to the above appearance, aroma and color of the *Chrysanthemums* are the main attractive features to researchers. Aroma plays a vital role in determination of quality and market price of *Chrysanthemums*. Traditional medicines from these plants have promising properties in improving liver function, decreasing inflammation. These perennial flowering plants are commonly available in Asia, northeastern Europe and most species originate from East Asia[1,2]. According to the literature survey more varieties of *Chrysanthemums* are mainly cultivated in china such as Shen-nong Sweet *Chrysanthemum*, Tender Huang-ju, Chamomile Flower, Hangzhou White *Chrysanthemum*, Florists *Chrysanthemum*, etc[3-5]. *Chrysanthemum* plants belong to Asteraceae family which has low molecular components include flavonoids[6], sesquiterpenes[7], triterpenes[8], and unsaturated fatty acids[9]. The volatile chemical compounds of *Chrysanthemum* essential oil are mainly composed of monoterpenes, sesquiterpenes, aldehydes, acids, esters and alcohols [10-12]. Recently, some researchers have paid

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Table 1. Recent studies on phytochemicals of *Chrysanthemum* spp.

Key findings	Reference
Recently, chrysanthemum flowers are known as a unique class of material which possess nutritional rich contents such as chlorophyll, carotenoids, soluble sugar, amino acid, vitamin C, flavonoid and chlorogenic acid at the time of bud stage and young flower stage. On the other hand, chrysanthemum flowers having great potential to produce active contents. Therefore both bud stage and young flower stage have been chosen as the best time for harvesting17.	Ma *et al*., 2016
A fundamental understanding study has been made for the optimal time of harvesting of chrysanthemum flowers. From the analysis it is concluded that at the early flower opening stage, the contents of flavonoids and volatile oil were higher. On the other hand the content of chlorogenic acid, luteolin, 3,5-O-dicaffeoyl quinic acid were higher in the middle of the flowers. From the overall analysis 50% -80% fowers blossoming stage was attributed as the optimal time for harvest18.	Wu *et al*., 2016
Generally, ±-pinene, ²-thujene, ±-terpinolen, ²-cubebene, caryophyllene, (Z)²-farnesene, (-)-spathulenol, linalool, camphor, camphene, 4-terpineol, Z-citral and 4-isopropyltoluene are typical aroma compounds covered with characteristic aroma of Chrysanthemum essential oils19.	Xiao *et al*., 2016
Totally, 21 compounds were isolated and identified from Leaves of "Chuju" Chrysanthemum morifolium named as octa-cosyl alcohol, ²-sitosterol, lupeol, ±-amyrin, daucosterol, ineupatorolide B, syringin, chlorogenic acid, petasiphenol, physcion, acacetin, eupatilin, quercetin, diosmetin, luteolin, apigenin, apigenin- 7-O-²-D-glucopyranoside, quercetin-3-O-²-D-glucopyranoside, luteolin-7-O-²-D-gluco pyranoside, apigenin-7-O-²-D- neospheroside, and acacetin-7-O-²-D-glucoside20.	Wei *et al*., 2015
Leaves of Chrysanthemum morifolium are the most widely used well known medicinal resource. The present study mainly foccusses to estimate the main bioactive components such as flavonoids, galuteolin, quercitrin, chlorogenic acid and 3 ,5-O-caffeoylquinic acid21.	Wang *et al*., 2015
An overall assessment using biochemical and differential proteomic data revealed that UV-B radiation could affect biochemical reaction and promote secondary metabolism processes in postharvest flowers22.	Yao *et al*., 2015
The flowers of twenty-three cultivars of Chrysanthemum contained the anthocyanins, cyanidin 3-glucoside and cyanidin 3-(3"-malonoyl) glucoside and the following carotenoids: lutein, zeaxanthin, ²-cryptoxanthin, 13-cis-²-carotene, ±-carotene, trans-²-carotene, and 9-cis-²-carotene23.	Park *et al*., 2015
A microwave-assisted extraction approach which is mainly based on ionic liquids of different chain lengths was successfully applied to the extraction of ten flavonoid glycosides from the flowering heads of Chrysanthemum morifolium Ramat. The main components were identified as flavonoid glycosides, including three luteolin glycosides, three apigenin glycosides, three kaempferide glycosides, and one acacetin glycoside24.	Zhou *et al*., 2015
Currently, chrysanthemum flowers becoming major research interest due to its major volatile compounds. Therefore, identification of the major volatile compounds and their relative concentrations in chrysanthemum flowers are essential. The major volatile compounds are camphor, ±-pinene, chrysanthenone, safranal, myrcene, eucalyptol, 2,4,5,6,7,7ab-hexahydro-1H-indene, verbenone, ²-phellandrene and camphene25.	Sun *et al*., 2015
In this study, three-channel liquid chromatography with electrochemical detection method was applied to the quantitative analysis of caffeoylquinic acids and flavonoids in four cultivars of Chrysanthemum morifolium flowers and their sulfur-fumigated products26.	Chen *et al*., 2015

Interestingly, one new octulosonic acid derivative, chrysannol A, along with 17 known compounds, was isolated from Chrysanthemum indicum flowers27.	Luyen *et al*., 2015
The appropriate UV-B radiation intensity did not decrease in flower yield, and could regulate phenylalanine ammonia lyase enzyme activity and increase active ingredients (anthocyanins, proline, ascorbic acid, chlorogenic acid and flavone) 1content in flowers of two chrysanthemum varieties28.	Yao *et al*., 2014
Five flavones were isolated from Chrysanthemum coronarium L., among them four of which were isolated for the first time from the genus Chrysanthemum. Two were the flavonoid aglycones 5,7-dihydroxy-3,6,4'-trimethoxyflavone and scutellarin-6,7-dimethyl ether. A new flavonoid glycoside, apigenin-7-O-[2"(6''-O-beta-D-acetylglucopyranosyl)]-6"-O-acetylglucopyranoside, along with two known ones, i. e. apigenin-7-O-(2"-O-beta-D-glucopyranosyl)-beta-D-glucopyranoside and 6-methoxy quercetin-7-O-beta-D-glucopyranoside, were identified29.	Abd-Alla *etal*, 2014
On the basis of the aroma-extract dilution analysis, the odour activity value and sensory evaluations, bicyclic monoterpenes (borneol, bornyl acetate and camphor) and ²-caryophyllene are considered to be the main aroma-active compounds of both extraction methods30.	Usami *et al*., 2014
A water-soluble polysaccharide (P2) with a molecular weight of 1.7×10(5)Da was isolated from the hot aqueous extract of flowers of the Chrysanthemum morifolium. Monosaccharide analysis revealed that P2 is an arabinogalactan containing arabinose (38.4% w/w), galactose (58.8% w/w), and glucose (2.8% w/w) in a ratio of 1:1.53:0.0731.	Liang *et al*., 2014
The nine phenolic compounds [(Z)-2-²-d-glucopyranosyloxy-4-methoxycinnamic acid (cis-GMCA), chlorogenic acid, (E)-2-²-d-glucopyranosyloxy-4-methoxycinnamic acid (trans-GMCA), quercetagetin-7-O-²-d-glucopyranoside, luteolin-7-O-²-d-glucoside, apigenin-7-O-²-d-glucoside, chamaemeloside, apigenin 7-O-(63 -O-acetyl-²-d-glucopyranoside), apigenin] and one polyacetylene (tonghaosu) from the flower heads of Chamomile/Chrysanthemum samples has been examined simultaneously by the new rapid UHPLC-UV-QTOF/MS method.32.	Avula *et al.,* 2014
Identification of chlorogenic acid, caffeic acid, 1,3-dicaffeoylquinic acid, 3, 5-dicaffeoylquinic acid, luteolin-7-O-beta-D-glucoside, 3,4-dicaffeoylquinic acid, linarin and luteolin in *Chrysanthemum indicum* was established using a high-performance liquid chromatography (HPLC) 33.	Dai *et al*., 2013
In GC-MS analysis 35 compounds were identified, and HPLC-PAD methods were reconfirmed and quantitatively determined 5 compounds (chlorogenic acid, luteolin-7-glucoside, linarin, luteolin and acacetin) in phytochemical studies. This is the first report to analyze the chemical constituents by integrates GC-MS with HPLC-PAD and investigated possible mechanisms34.	Wu *et al*., 2013
Analysis of essential oil from Flower and leaf were determined 38 and 36 components, representing 96.4 and 91.0% of the total oil composition, respectively. The most important compound in flower oil were camphor (47.64%), bornyl acetate (11.87%), and nojigiku alcohol (6.29%), whereas those in leaf oil were camphor (39.14%), nojigiku alcohol (10.76%) and ³-muurolene (7.02%). 13 Aroma-active compounds from flower oil and 12 in leaf oil were determined by GC-O analysis 35.	Usami *et al*., 2013
The combination of HPLC/UV and PCA in pressurized hot water extraction can be used favorably as a green and productive approach for characterization and quality control of ubiquitous functional food such as chrysanthemum36.	Liu *et al*., 2013

Table 2. Recent studies on biological activities of *Chrysanthemum* spp.

Key findings	Reference
Owing to non-toxic and abundance snow chrysanthemum antioxidants become a better alternative to Chrysanthemum morifolium. Snow chrysanthemum possesses higher antioxidant activity compared to Chrysanthemum morifolium. Therefore the research interest arises in snow chrysanthemum due to its excellent antioxidant activity[45].	Chen *et al*., 2016
Nowadays, Skin diseases induced by UV radiation such as skin cancer and photoaging become a global concern. The active components in wild chrysanthemum extract are a promising candidate in drug development for above mentioned skin diseses[46].	Sun *et al*., 2016
It is important to mention here that, the essential oil of the Jordanian Chrysanthemum coronarium L. (garland) which is isolated from flower heads having excellent antimicrobial activities against both Gram-negative and Gram-positive bacteria. According to the survey globally more than 1 million people get colon cancer every year. Hence, more effort has been made by researchers towards sensitivity of oil treatments to colon cancer. [47].	Bardaweel *et al*., 2015
It is noteworthy to mention here that, 3,5-diarylpyrazole analogues become one of the best alternatives to bioactive compounds, as it exhibit several advantages like A^2 aggregation, neuroprotective activity which are useful in Alzheimer's disease treatment [48].	Wu *et al*., 2015
Interestingly, water-soluble polysaccharide scavenges the DPPH radicals which are caused by H_2O_2. The anti-oxidative analysis showed PC12 cells damage has been prevented by water-soluble polysaccharide. Hence, it is found as potential natural antioxidant[49].	Zheng *et al*., 2015
Chrysanthemum indicum ethanol extract could attenuate cisplatin-induced nephrotoxicity and might be a beneficial agent for acute renal failure management[50].	Kim *et al*., 2015
Chrysanthemum morifolium flower extract successfully absorbs luteolin and luteolin monoglucoside, luteolin monoglucuronide and leads to better circulation in humans[51].	Yasuda *et al*., 2015
The elevated adiponectin levels lead to amelioration of insulin resistance and the corresponding hypoglycemic effects. Therefore, a hot water extract of edible Chrysanthemum morifolium treated as a potential food for type 2 diabetes[52].	Yamamoto *et al*., 2015
In the case of Proanthocyanidins extracted from Kunlun Chrysanthemum flowers, antiaging effect on Drosophila has been noted. In the present study PKCF is found as a suitable candidate in health care, medicine, and cosmetics[53].	Jing *et al*., 2015
Chrysanthemum indicum extract could have a potential therapeutic role in bone-related disorders due to its dual effects on osteoclast and osteoblast differentiation[54].	Baek *et al*., 2014
The supercritical-carbon dioxide fluid extract from Chrysanthemum indicum Linne plays a vital role against lipopolysaccharide-induced acute lung injury (ALI) in mice. Thus, it can be referred as a potential therapeutic drug for ALI. Its mechanisms were at least partially associated with the modulations of TLR4 signaling pathways[55].	Wu *et al*., 2014
The oral intake of peptide mixture and the aqueous extract of Chrysanthemum morifolium had synergistic antimelanogenic and antioxidative effects in UV-irradiated mice[56].	Gui *et al*., 2014
According to the literature survey, it can be concluded that fifty compounds were identified from essential oils of the leaves, stems and roots of Chrysanthemum trifurcatum (Desf.) Batt. and Trab. var. macrocephalum. The oil and methanolic extact from C. trifurcatum leaves showed a great potential of antibacterial effect against Bacillus subtilis and Staphylococcus epidermidis, with an IC50 range of 31.25-62.5 µg/ml[57].	Sassi *et al*., 2014
The water fraction of Chrysanthemum zawadskii extracts stimulated the	Li *et al*., 2014

differentiation and proliferation of pluripotent epidermal matrix cells in the matrix region and epithelial stem cells found in the basal layer of the epidermis. The water fraction of Chrysanthemum zawadskii extracts may be developed as a therapeutic agent for the prevention of hair loss[58].	
Chrysanthemum indicum is widely used to treat immune-related and infectious disorders in East Asia. C. indicum flower oil contains 1,8-cineole, germacrene D, camphor, ±-cadinol, camphene, pinocarvone, ²-caryophyllene, 3-cyclohexen-1-ol, and ³-curcumene. Intake of C. indicum flower oil produces no acute oral toxicity, bone marrow micronucleus, and bacterial reverse mutation[59].	Hwang *et al*., 2014
Chrysanthemum zawadskii Herbich var. latilobum Kitamura ethanol extract negatively regulates osteoclast differentiation. It act as a potential therapeutic candidate for the treatment of various bone diseases, such as postmenopausal osteoporosis, rheumatoid arthritis, and periodontitis[60].	Gu *et al*., 2013
Chrysanthemum zawadskii extract attenuates 2-deoxy-D-ribose-induced cell damage in osteoblastic cells and may be useful for the treatment of diabetes-associated bone disease[61].	Suh *et al*., 2013
The hot water extract of Chrysanthemum indicum L. flower inhibited bioactivation of CCl4-induced hepatotoxicity and downregulates CYP2E1 expression in vitro and in vivo studies[62].	Jeong *et al*., 2013
Linarin and its aglycone, acacetin from flowers or leaves of Chrysanthemum boreale exhibited sedative and anticonvulsant activities in the present in vivo assays. It can be considered that linarin is one of the promising active compounds effective against anxiety, insomnia, and stress, with acacetin as its active moiety[63].	Nugroho *et al*., 2013
The Chrysanthemum lavandulifolium extract, which includes chrysoeriol, sudachitin, and acacetin, has challenging antibiotic effects on Escherichia coli O157:H7 (E. coli O157). The multi-target efficacy of the Chrysanthemum lavandulifolium extract may indicate the potential for the development of more effective and safer drugs that will act as substitutes for existing antibiotics[64].	Kim *et al*., 2013

more attention to characterize the aroma compounds of flowers and essential oils. Xia et al.,[13] used GC–MS to analyze the volatile chemical composition from *Chrysanthemum*. *C.morifolium* is a most widely used hardy variety, available in many colours which are a better choice for gardens.

Phytochemicals of *Chrysanthemum* spp.

Phytochemicals are biologically active chemical compounds which are derived from plants. They have many health benefits for humans further than those attributed to macronutrients and micronutrients. They play a key role to protect plants from pathogenic infections and damage. Plants have different types of phytochemicals such as Phenolic Acids, Flavonoids and Lignans which contribute to the plant's color, aroma and flavor. Phytochemicals accumulation takes place in different parts of the plants, such as roots, stems, leaves, flowers, fruits and seeds[14]. More than 4,000 phytochemicals have been cataloged[15] and are classified by protective function, physical characteristics and chemical characteristics[16]. From the survey of more than 80 research papers it is estimated that About 150 phytochemicals have been studied in detail. *Chrysanthemum* spp. Leaf contains octa-cosyl alcohol, ²-sitosterol, lupeol, ±-amyrin, daucosterol, ineupatorolide B, syringin, chlorogenic acid, petasiphenol, physcion, acacetin, eupatilin, quercetin, diosmetin, luteolin, apigenin, apigenin- 7-O-²-D-glucopyranoside, quercetin-3-O-²-D-glucopyranoside, luteolin-7-O-²-D-gluco pyranoside, apigenin-7-O-²-D- neospheroside, and acacetin-7-O-²-D-glucoside. Most of the *Chrysanthemum* spp flowers contain anthocyanins, cyanidin 3-glucoside and cyanidin 3-(3"-malonoyl) glucoside and carotenoids: lutein, zeaxanthin, ²-cryptoxanthin, 13-cis-²-carotene, ±-carotene, trans-²-carotene, and 9-cis-²-carotene. The major volatile compounds present in the plants are camphor, ±-pinene, chrysanthenone, safranal, myrcene, eucalyptol, 2,4,5,6,7,7ab-hexahydro-1H-indene, verbenone, ²-phellandrene and camphene. Recent studies reported by several researchers about phytochemicals found in leaves,

flower and essential oil from *Chrysanthemum* spp are showed in table 1.

Biological activities of *Chrysanthemum* spp.

The phytochemicals play a significant influence to prevent diseases and promoting health has been studied extensively to establish their efficacy. Identification and isolation of the chemical components, establishment of their biological potency carried out by many researchers both in vitro and in vivo studies have been analyzed through literature survey. From this review, the experimental details reported in literatures which are done in animals, through epidemiological and clinical-case control studies in man are clearly described in table 2. Overproduction of free radicals can induce many human diseases such as diabetes, cancer, stroke, rheumatoid arthritis and atherosclerosis[37-39]. Antioxidants can alleviate the oxidative stress, which is beneficial for human health[40]. However, some currently used synthetic free radical scavengers have been demonstrated various side effects[41,42]. Therefore, functional foods become a promising source of natural antioxidants[43,44]. It is noteworthy to mention here that *Chrysanthemum* spp. has many health and medicinal properties such as Antioxidant, skin cancer, antimicrobial activities and various bone diseases. Recent studies on biological activities of *Chrysanthemum* spp reported by various researchers are shown in table 2

CONCLUSION

The analysis based on this detailed literature survey it is concluded that *Chrysanthemum* spp is the best choice for researchers to develop multifunctional drugs. Among various medicinal herbs *Chrysanthemum* spp is one of the non-toxic, biocompatible and eco-friendly herbs. In order to develop more effective drugs in future for various pathogens one should recognizes phytochemicals and their performances. This paper presents an overview of *Chrysanthemum* spp phytochemicals and their biological activities in recent years reported by various research groups. Many research works have been done on phytochemicals of flowers and leafs of *Chrysanthemum* spp plant. But more innovative research work still required find new phytochemical compounds which lead to develop new pharmaceutical compounds.

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