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A BRIEF PHYTOCHEMICAL INVESTIGATION AND PHARMACOLOGICAL USES OF CITRUS SEED – A REVIEW

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Abstract

Citrus fruits are more important in all over the world. They are well known as nutritional and medicinal property. Lemon is one of the most common citrus fruit. Lemons are typically grown from seeds, which are planted and developed as trees. Trees of citrus fruit can stand from 10 feet to 20 feet tall, and can produce fruit for more than 30 years. Citrus seeds contain certain compounds with various level of bitterness. These compounds have been tested against insects and proved to be effective. Oil is extracted from citrus seeds to use in skin lotions and shower gels. The hexane-extracted oil content of citrus seeds ranged from 27.0 to 36.5%. The protein, fiber and ash contents were found to be 3.9–9.6%, 5.0–8.5%, and 4.6–5.6%, respectively. The extracted oils exhibited an iodine value of 99.9–110.0; refractive index (40 C), 1.4639–1.4670; density (24 C), 0.920–0.941 mg/mL; saponification value, 180.9–198.9; unsaponifiable matter, 0.3–0.5%; acid value (mg KOH/g of oil), 0.5–2.2 and color (1-in. cell) 1.4–3.0R + 15.0–30.0Y. Consuming citrus seeds can kill parasites like threadworms. Plump, bright and flavorful, lemons serve as the stars in many beverages and meals. But the tiny seeds are eventually responsible for all of those flavorful tarts, cold summer drinks and seafood toppers. The main characteristic of citrus seed is thorny branches, white flowers with purple edges. Medicinal property of lemon seed contains antioxidant activity, antifertility activity, hepato protective activity and others. Extracts from citrus seed were investigated for the radical scavenging activity and apoptotic effects in human breast adenocarcinoma (MCF-7) cells and non-malignant breast (MCF-12F) cells for the first time. This review presents update information gathered on scientifically screened plant parts used for different activity.

Keywords: *Citrus, Lemon, Anti-fertility, Hepatoprotective*

Introduction

Citrus genus of plants belonging to the Rutaceae family, and yielding pulpy fruits covered with fairly thick skins. Economically important plants in this group include the lemon (C. limon), lime (C. aurantiifolia), sweet orange (C. sinensis), sourorange (C.aurantium), tangerine (C.reticulata), grapefruit (C.paradisi), citron (C.medica), and shaddock (C. maxima). Lemon (Citrus × limon) is a hybrid of the plant genus Citrus, as well as the common name of the popular edible fruit of this small tree. The citrus fruit known in ancient times in Europe since the lemon (Citrus limon), lime (Citrus × auantiifolia), pomelo (Citrus maxima) and bitter orange (Citrus × aurantium L.) were all introduced in Europe by the Muslims via the Sicily and Iberian Peninsula. The main characteristic of lemon plant is thorny branches and white flowers with purple edges, the acidic, juicy fruit is oval (shaped like egg), has an aromatic rind that is yellow when ripe (green as immature and under certain environmental conditions, Fig-1), and has a prominent bulge or nipple on the blossom end [1].

The plants of most species of Citrus are large evergreen shrubs or small trees, 5–15 m tall [2]. Citrus are recognized as one of the world's major fruit crops. These are produced in many countries all around the world with tropical or subtropical climate. Brazil, USA, Japan, China, Mexico, Pakistan, and countries of the Mediterranean region are the major citrus producers. Citrus production worldwide is around 105 million metric tons (MMT) per annum with Brazil being the largest producer of 19.2 MMT followed by the United States. However, the United States leads the world with an average yield of 30 tons per hectare followed by Brazil and China with 20–25 and 18–20 tons, respectively. Pakistan with an annual production of 1.76 MMT of citrus fruits stands among the ten top citrus producing countries of the world [3,4]. In addition to large scale consumption, the citrus fruits are mainly processed to produce juice and the waste of this industry such as peels, seeds and pulps which represent about 50% of the raw processed fruit are a potential source of valuable by-products [5]. Citrus fruits are of high-economic value because of their multiple uses, such as in the food industry, cosmetics and folk medicine [6-8]. The citrus seeds, commonly considered as agro-industrial waste, are a potential source of oil. Reda et al. studied the characteristics of Citrus limonia and C. limon seed oils from Brazil [9]. Habib et al. investigated the chemical composition of Egyptian citrus seeds as potential sources of vegetable oils [10]. Ajewole and Adeyeye reported the characterization of Nigerian citrus seed oils [11]. Trandjiiska and Nguyen studied the triacylglyceride composition of seed oils of citrus fruits from Vietnam [12]. Literature revealed that citrus seeds oils are a good source of unsaturated fatty acids (FAs) [8]. The global demand for vegetable oils and fats (approx. 125 million tons per annum) has increased due to rapid industrial and uncontrolled human population growth. The outcome, not only in the form of expenditures of huge amounts of valuable foreign exchange for importing vegetable oils and fats, nevertheless, has resulted in a deficiency in people's fat intake in many countries of the developing world. In view of the rapidly growing edible and oleo-chemical industrial demands, the search for some alternative sources of additional vegetable oils and fats with nutritional and pharmaceutical attributes has to play a vital role [13]. As a result of large scale citrus fruit consumption and processing, a huge quantity of citrus seeds, generally discarded as an agro-industrial waste is generated every year which could be favorably utilized for production of oil and value-addition. This means there is a need to carry out a comprehensive study to extract and characterize citrus seed oils. To our best understanding, no such detailed studies on the composition and characteristics of citrus seeds and seed oils from sub-continental regions.

Generally, Citrus species are grown in tropical and sub-tropical climates where the rainfall is limited, so irrigation is required to sustain the plant growth, creating salinity problems. Citrus species are very sensitive to salinity. Salinity affects seed germination, plant growth, fruit yield and it causes nutrient imbalances in the plants. The most harmful constituent of saline soils is NaCl. Cleopatra mandarin, Rangpur lime, Citrus macrophylla, Sunki mandarin and Shekwasha mandarin are rootstocks tolerant to salinity and rough lemon and trifoliate orange are sensitive. However, variation in salt

tolerance exists among the strains of various citrus rootstocks [14].

The citrus seeds are rich in nutrients and contain many phytochemicals; they also can be efficiently used as drugs or as food supplements. There is an increase in the number of antibiotic-resistant pathogens, and there is always a search of an alternative drug that is regarded as safe. Phytochemicals are secondary metabolites and help shield us from various ailments and disorders [15]. Addition of citrus seed extract was effective in reducing lipid oxidation in both cooked and raw broiler meat under refrigeration. Thus, oxidative stability of chicken meat can be prolonged for 12 days with citrus seed extracts under refrigeration storage [16].

Citrus fruits are the main winter fruits consumed in the Mediterranean diet, so they are the main source of dietary flavonoids. The possible beneficial effects are due, not only to the high amounts of vitamins and minerals, but also to the antioxidant properties of their flavonoids. Dietary flavonoids may help to supplement the body antioxidant defences against free radicals. These compounds' possible beneficial effects are due to their antioxidant activity, which is related to the development of atherosclerosis and cancer, and to anti-inflammatory and antimicrobial activity [17].

Lemon peel contained crude fibres (15.18%), crude fat (4.98%), and protein (9.42%). Ash content of lemon peel is 6.26% [18]. Citrus seeds contain from 26 to 42% of oil and are a good source of K, Ca, Na, Fe and Mg (El-Adawy et al., 1999). Several phytochemicals may be detected in edible seed oils including tocopherols, carotenoids, phenolic and polyphenolic compounds, and special fatty acids such as α-linolenic acid [19]. Lemon juice is about 5% acid, which gives lemons a sour taste and pH of 2 to 3. A lemon tree can grow up to 10 meter (33 feet), but they are usually smaller. The branches form an open crown and are thorny. The leaves are green, elliptical-acuminate and shiny. Flowers have a strong fragrance and are white on the outside with a violet streaked interior. On a lemon tree, flowers and fruits can be found at the same time.

The herbal and medicinal value of plants appears in all early records of human activity, from the Chinese 5000 years ago, to the herbalists, apothecaries, pharmacists, and physicians of all succeeding generations, to modern use of herbs, their extracts, and synthetic products to treat minor ailments and diseases today. It is not surprising that the taxonomic family to which citrus belongs, the Rutaceae, which includes approximately 160 genera and 1,700 species, has been used in herbal medicine [20].

Lemon and lime trees should not be grown in cooler winter areas, because they are more sensitive to winter cold than other citrus fruits. The largest producer's places are Italy and the United States. Lemons are commercially grown in cooler summer or moderate-winter coastal Southern California in the United States, since sweetness is neither attained nor expected in retail lemon fruit. Other top producing nations include Greece, Spain and Argentina.

Botanical classification of lemon:

Kingdom	: Plantae
Subkingdom	: Tracheobionta
Superdivision	: Spermatophyta
Division	: Magnoliophyta
Class	: Magnoliopsida
Subclass	: Rosidae
Order	: Sapindales
Family	: Rutaceae
Genus	: Citrus L.

HISTORY

Natural and cultivated citrus hybrids include commercially important fruit such as oranges, grapefruit, lemons, limes, and some tangerines. The lemon was firstly introduced into southern Italy in 200 A.D. and spread to Iraq and Egypt by 700 A.D. Lemon was introduce in the Spanish to the Island of Hispaniola in 1493 and sometime the first settlement of St. Augustine, Florida. Lemon was introduced into California in 1751-1768 [21]. Lemons are thought to have originated in China or India, cultivated in these regions for about 2,500 years.

Citrus plants are native to subtropical and tropical regions of Asia and the Malay Archipelago, and they

were first domesticated in these areas. Some citrus species have been present in the Mediterranean basin for centuries. This group of species has reached great importance in some of the Mediterranean countries, and in the case of orange, mandarin, and lemon trees, they found here soil and climatic conditions which allow them to achieve a high level of fruit quality, even better than in the regions from where they came.[22]

GEOGRAPHICAL DISTRIBUTION

It is indigenous to North India, but cultivated on a very large scale in countries like Sicily, Italy and Spain. It is also cultivated in India, Florida and California. In Bangladesh, most of the citrus species is cultivated commercially.

Methods

We have studied a large number of research and review articles related to citrus fruits and seeds. We have also collected data from authentic websites and finally summarize the findings of phytochemicals and medicinal uses of citrus seeds.

Results and Discussion

Phytochemical Investigation:

Various phytochemicals and phenolic contents present and uses of citrus seed found from different literature are summarized in table 1, table 2 and table 3.

Pharmacological Uses:

Pharmacological uses of various citrus seed is discussed below:

Anti-fertility effect:

According to Kulkarni et al (2004) many time plant extracts have been investigated for their anti-fertility effect. Among all citrus species, Citrus limonum was selected for antifertility test. For this test, alcoholic, petroleum ether and aqueous extract of Citrus limonum seeds were experimented in female albino mice. After post-ovulatory test the extract were administered orally for 7days 4% gum acacia was received by control group. On 10th day of pregnancy the animal were examined for implantation site and number of pumps delivered at term for each group was recorded. The alcoholic extract showed effective anti-fertility effect in compared with petroleum either and aqueous extracts. The fraction of these extract again subjects to tested. Ethyl acetate fraction (12-25) showed more anti-fertility effect. The alcoholic extract and its ethyl acetate fraction (12-25) were showed the similar mechanism as anti-zygotic agent. Complete restoration of fertility was resulted from withdrawal of test drug. So, the ethyl acetate fraction of alcoholic extract of lemon seed showed anti-fertility effect in female albino mice through its anti-zygotic action.[24]

Anti-oxidant effect:

According to International Conference on AABES-2015, citrus fruits have a lot of biological effective compounds that have ability to attack radical free and work as natural anti-oxidant. Citrus is one of the important plants economically. Five species of citrus such as C. aurntium, C. limon, C. paradise, C. reticulate, C.sinensis were selected to investigate antioxidant activity. High quantities of phenolic compounds are present in extracts of citrus seed which exhibit anti-oxidant activity, total flavonoids, free radical activity and reducing power. These constituents helps the seed extracts to be as effective natural anti-oxidants. [25]

Chemo-preventive and Cytotoxic effect:

Consumption of fruits and vegetables may not have a significant influence in reducing the risk for breast cancer (Van Gils et al., 2005) [26]. However, several bioactive compounds derived from fruits and vegetables, including flavonoids (Conklin et al., 2007) [27], polyphenols (Thangapazham et al., 2007)[28], and vitamins (Ooi et al.,2010; Richard et al., 2010) [29-30], were evaluated for inhibition of breast cancer cell growth and metastasis in in vitro and in vivo model systems. Citrus species received attention due to bioactive compounds in them. Bio-active compounds from citrus, such as limonoids, flavonoids (naringin), and carotenoids (lycopene, lutein), were determined to suppress the growth rate of human breast cancer (Tian et al., 2001) [31]. Bioactive components in lemon seed extracts could be a good source of antioxidants and induce apoptosis in MCF-7 breast cancer cells. Separated seed powder was extracted with ethyl acetate, acetone, methanol and MeOH:water (80:20). LC-MS and HPLC analysis was used to identify and

quantified the chemical constituents. The MeOH:water (80:20) extract showed the highest (29.1%,P<0.01) inhibition of MCF-7 cells in MTT assay. Treatment of MCF-7 cells with MeOH:water extract induced DNA fragmentation , PARP cleavage , increased level of Bax and cytosolic cytochrome C , decreased level of Bcl2. Resulting in induces apoptosis of MCF-7 cells that lead to inhibition of proliferation . Result suggest that aglycones and glucosides of the limonoids and flavonoid present in MeOH:water extract may potentially serve as a chemopreventive agent for breast cancer.[32]

Hepatoprotective effect:

According to Naunyn-Schmiedeberg's Arch Pharmacol (2014) C. aurantium var. bigardia derived limonin is effective as hepatoprotective agent in hepatic injury. We have experimented the effects of limonin in two dose levels (50 mg/kg and 100 mg/kg) which was isolated from the dichloromethane fraction of seeds of Citrus aurantium var. bigardia. That was applied on D-galactosamine induced hepatic toxicity in compared with standard silymarin(100mg/kg) , using a well-established rat model of acute hepatic inflammation. Hepatic damage (Elevated liver enzyme activities and total bilirubin) and hepatic inflammation (TNF-α , infiltration of neutrophils) , oxidative stress and expression of TLR-4 but not TLR-2 resulting in the treatment of rats with D-GalN.DDue to preventive strategy , limonin was administered before injection of D-GalN. The effects of limonin and silymarin were same. The higher dose of limonin (100mg/kg) more effective for AST and bilirubin. The lower dose of limonin (50mg/kg) can give better action against oxidative stress, hepatic damage in compared to higher dose. The result support that C. aurantium derived limonin have more potent action against acute hepatic injury, liver toxicity associated with inflammation and tissue injury via attenuation of inflammation and reduction of oxidative stress.[33]

Cell apoptosis:

According to Tumor Biol. (2016), cancer cell death can induced by using natural products through apoptosis, autophagic cell death and necroptosis. The aim of this study were to identify the activity of Citrus seed extract contents in human hepatocellular carcinoma HepG2 cell apoptosis. Citrus seed contain bioflavonoids with the bioactivities on apoptosis induction in human hepatocellular cancer cells. Neohesperidine, hespiridine and naringin are active flavonone glycosides. Hesperidin can induced cell death in hepatic cancer cells. The HepG2 cell death was apoptosis in a dose response manner because of externalization of phosphatidylserine without propidium iodide staining to the DNA, which was detected by annexin V-FITC/PI and flow cytometry. This cell apoptosis can be performed via mitochondrial and death receptor pathways. The HepG2 cells treated by hesperidin that loss mitochondrial transmembrane potential. Caspase -9, -8 and -3 activities were activated and increased in HepG2 cell treated by Hesperidine. Flavonoids from Citrus seeds are beneficial and can be developed as anticancer drug or food supplement.[34]

Effect against Dengue Fever Mosquito:

According to Waseem Akram et al. (2010) Citrus seed contain different compounds with varied level of bitterness. These compounds have been tested against insects and proved to be effective. In laboratory, different citrus seed extracts were tested against Aedes albopictus larvae. These extracts provided satisfactory result. 10 varieties of citrus extracts carried out to test against 4th instar larvae of dengue fever mosquito, Aedes albopictus. The extracts from Citrus jambhiri and Citrus limon were more effective as larvicides with lowest LC50 (119.993 and 137.258 ppm respectively, after 24h of exposure and 108.85 and 119.853 ppm respectively, after 48h of exposure) and LT50 values (2.51 and 4.91h, respectively) and highest percent mortalities (95.6 and 88.9% respectively), after 24 hours of exposure. The results indicate that Citrus jambhiri and Citrus limon being the most effective in terms of LC50, LT50 and percent mortalities. Citrus-seed extract are environment friendly and can be used for managing A. albopictus larvae.[35]

Haematopoetic effect:

According to Adeneye et al. (2008), Anaemia is one of the major health problems which affecting more than 30% of population in worldwide. Citrus paradise Macfad (Rutacaea) is known as grape fruit. The aim of this study is to evaluate the haematinic property of methanol seed extract of Citrus paradisi Macfad.

This affect can be identified by chronic administration at the oral dose of 100-600 mg/kg/day of the extract on the haematological parameters in normal young adult female Wistar rats. Elevated level of total leucocyte count (TLC), lymphocyte differentials (Lymph.), red blood count (RBC), haemoglobin con-centration (Hb), packed cell count (PCV), mean corpuscular volume (MCV), mean corpus-cular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC) and platelet count (PL) were resulting from the 30days of oral administration with graded doses. Number of neutrophil and monocyte differentials was decreased in the treated rats.[36]

Grapefruit contains ascorbic acid [37] and folates [38] which are known to be essential for body tissue formation and maintenance including blood, blood vessels and bone [39]. So the extract may account for the significant improvement in the haematological factors due to presence of two vitamins. The study demonstrate that the methanol extract of Citrus paradisi Macfad can be used in the treatment of blood deficiency.

Conclusion

As citrus seeds remains a natural, more economical, efficient and readily available sources of drugs over the conventional synthetic drugs, their therapeutic properties is still very much under maximize. Citrus seeds are highly enriched with a lots of nutritional and health benefits. They can actually help prevent and cure some diseases. Citrus flavonoids have potential antioxidant (prevents aging), anti-cancer, antiviral, anti-inflammatory activities, effects on capillarity, and cholesterol-lowering ability. So the citrus seeds are believed to be the bioactive ingredients of Citrus species responsible for these pharmacological activity.

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Table 1. Phytochemical analysis for orange and lemon seed [23]

Phytochemicals	**Orange seed**	**lemon seed**
Phlobatannins	+	++
Carbohydrates	+	++
Flavonoids	+++	+++
Alkaloids	+++	+++
Terpenoids	+	+

Table 2: Total phenolic content [23]

Orange seed extract	36 mg GAE/g
citrus seed extract	33 mg GAE/g

Table 3: Proximate composition (%) of seeds of different citrus species [23]

Constituents	*Citrus limetta*	*Citrus paradisi*	*Citrus sinensis*
Oil content	29.76 ± 0.59	36.54± 0.36	27.00 ± 0.81
Protein content	6.43 ± 0.18	3.90 ± 0.15	5.56 ± 0.25
Fiber content	5.00 ± 0.20	8.50 ± 0.20	6.90 ± 0.17
Ash content	5.50 ± 0.11	5.03 ± 0.15	4.60 ± 0.13

Values (expressed on dry weight basis) are mean ± SD of three seeds of each citrus species, analyzed individually in triplicate Different letters in superscript indicate significant differences within citrus species.

Figure 1: Citrus Fruits and Seeds