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Citrus peel: An essential source of bioactive compounds and nutraceutical constituents

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Abstract
Fruit waste contains a variety of bioactive substances, including colours, polyphenols, polysaccharides, and many other phytochemicals. Using fruit "leftovers" as a foundation for bioactivities that could become new foods or food ingredients also generates new business prospects, increasing the characteristics of the circular economy. The citrus peel contains various bioactive compounds including carotenoids, flavonoids, flavones and flavonols, essential oil (terpenes and limonoids), pectin and flavanones. Also, they have various industrial application Animal feed, Organic fertilizer, Activated citrus peel extract, Preparation of citrus peel packaging films, biorefinery of orange peel, ethanol, industrial enzymes, paper pulp supplement and single cell protein. Microwave assisted technique is the most commonly used technique for extraction of bio-active compounds. The review highlights the diseases that can be prevented using the sample of bio-active compounds extracted. Also, there was a discussion on what are the future aspects of citrus waste industry. Each bioactive compound serves a distinct and important biological purpose in the management of specific illnesses. For instance, the most important phenolic chemicals to use in the food and pharmaceutical sectors are tannins, phenolic acids, and flavonoids. Numerous biological actions, such as antioxidant, antibacterial, anticancer, anti-inflammatory, and antidiabetic properties, are displayed by these bioactive substances. Citrus peel is thus a prospective source of foods with beneficial properties. It can also be used as a thickening, flavouring, and food colouring ingredient. Citrus peel, a waste product of the citrus processing industry, thus demonstrates potential economic benefits by returning to the food processing chain as an additive and offering sustainable and creative approaches to the utilisation of food waste. Various innovative techniques for extraction bioactive components from fruit residue are highlighted in this review.

Keywords: Orange peel, microwave assisted extraction, bioactive compounds, extraction techniques, health benefits

Introduction

Citrus fruit is among most widely produced crops in the world, with lemons, grapefruits, and oranges being among the most significant varieties. Citrus fruits contain range of bioactive compounds, such as vitamin C, limonoids, folic acid, potassium, dietary fiber, etc., that can improve human health ((Hou *et al*., 2019; Satari & Karimi, 2018) [72-73]. Yet only fruit contains the limonoids that belongs to tetranortriterpenoids with an attached furan ring. Limonoids can exist as "tasteless" glucosides that dissolve in water as well as "bitter" aglycones that are insoluble in water (Poulose *et al*., 2006) [74]. Antioxidants present in citrus peels has been shown to have a variety of biological actions in recent years, including anti-cancer, anti-inflammatory, anti-obesity, immune-modulating, anti-osteoclastogenic, anti-viral and neuroprotective effects. Therefore, limonoid is studied thoroughly. (Zang *et al*., 2020) [45].

The production of citrus, that is one of the significant fruit crop in the world, was expected to be 89 million tonnes in 2014. 26% of juice production is from citrus fruits (Khan *et al*., 2021) [64]. Estimated at 15 106 tonnes, industrial citrus coproducts mostly consist of seeds, peels, and pulp residue. The inside spongy component known as albedo, which is high in pectin and phenols, and the exterior surface known as flavedo, is well known for composition of carotenoids and essential oils present. The vacuoles of tissues contain phenolic chemicals, which are secondary metabolites produced by plants (Ignat *et al*., 2008) [135]. These play a major role in defence system of plant against pathogenic or UV radiation. They might also function as phytoalexins and contribute to the sensory and organoleptic qualities of fruits and vegetables (Colour, taste, and astringency). (Ghasemi *et al*., 2009) [78]

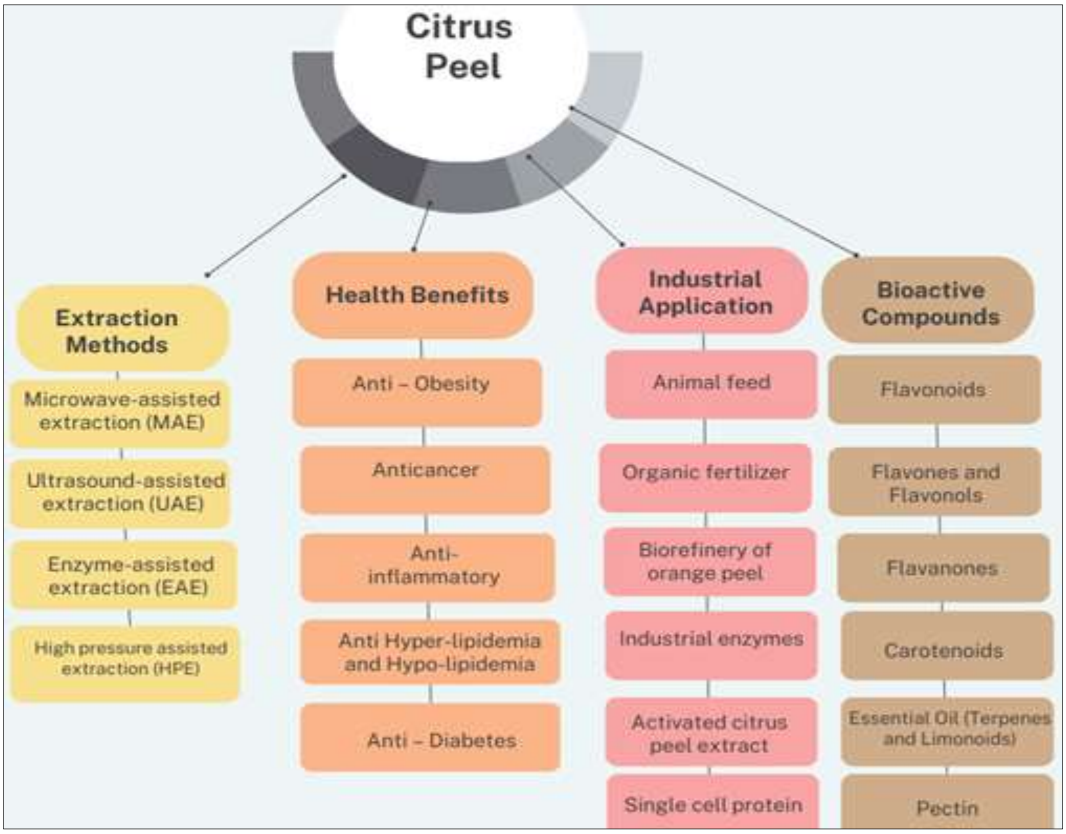

Fig 1: Uses of Citrus Peel

Phenolic compounds in citrus peel have been used to create products good for health. They can be a source of natural additives, sweeteners (hesperdin and neohesperidin), colourants (anthocyanins), and for their characteristic bitter flavour in some beverages (naringin). (Addi *et al*., 2021) [136]

Citrus peel and citrus juice residues are processed to be stabilised before being used in diverse applications. They are more susceptible to microbial degradation or spoilage due to more moisture content (70%). Citrus peel stabilisation procedures frequently involve heat (Putnik *et al*., 2017) [17], although heat can harm the citrus' thermosensitive components. The primary phenols in citrus, known as flavonoids, can be lost during processing since they are susceptible to factors including temperature, light, and exposure duration. (Nayak *et al*.2005) [137] evaluated how temperature and nonthermal mechanisms affect the phenolics' kinetics of stability and degradation as well as the antioxidant activity of fruits, vegetables, and cereals. In comparison to individual antioxidant components, complex natural combinations have a stronger antioxidant activity in foods. This was attributed to a synergistic effect. Various thermal and non-thermal processes helps in reduction of antioxidant activity of phenolic compounds via enzymatic oxidation, breaking of covalent bonds, or alteration of compound structural form. Nevertheless, antioxidant activity may rise when treatment is going on, which can be related to the synthesis of novel molecules with potent antioxidant activity phase. (Pathaw *et al*., 2020) [14]

The food industry primarily uses citrus, an important crop, to produce fresh juice or beverages with citrus as an ingredient. Every year, extremely enormous waste, such as peels, are created throughout the production (Wedamulla *et al*., 2022) [21]. Citrus (By product) wastes have historically been valorized as molasses for the producing animal feed, including pectin (a fibre), and fuel. Due to the vast volume of peel produced and the high concentration of phenolic compounds in citrus peels, natural flavonoids can come utilized from citrus byproducts formed by processing. Furthermore, whereas flavonoids are common, citrus contains a number of chemicals that are rarely found in plants, including flavanones, polymethoxylated flavones and flavanone glycosides (Khan, 2021) [64].

The main concern in various laboratories and industries is the selection of appropriate method for the extraction natural bioactive compounds (NBCs) in order to prevent human diseases as well as to address other demands. These substances effectively interact with proteins, DNA, and other biological molecules to achieve the desired results, which could be used to develop therapeutic medicines derived from natural products (Ajikumar *et al*., 2008) [75]. Plants typically create secondary metabolites as their bioactive substances. Some of these secondary metabolites are said to be bioactive because they have an impact on biological systems. Bioactive compounds can easily be termed as secondary metabolites that provide a pharmacological effect to living beings (Bernal *et al*., 2010) [76]. The screening of NBCs has undergone a radical transformation as a result of recent technical advancements and the development of innovative approaches to enhance production, detection, separation, and/or characterization (Van Lanen *et al*., 2006) [77]. The right extraction technique is largely what determines the results of qualitative and quantitative analyses of bioactive chemicals from plant sources (Smith *et al*., 2003) [79]. Although the advent of contemporary chromatographic and spectrometric techniques has made the analysis of bioactive compounds simpler than ever before, the result will be declared and verified by extraction process, variables noted, along with the precise nature of the flora components. Solvent, pressure, temperature and time are among matrix characteristics of the plant. These are the most frequent variables influencing extraction operations (Hernández *et al*., 2008) [80].

Bioactive Compounds of Citrus Fruits

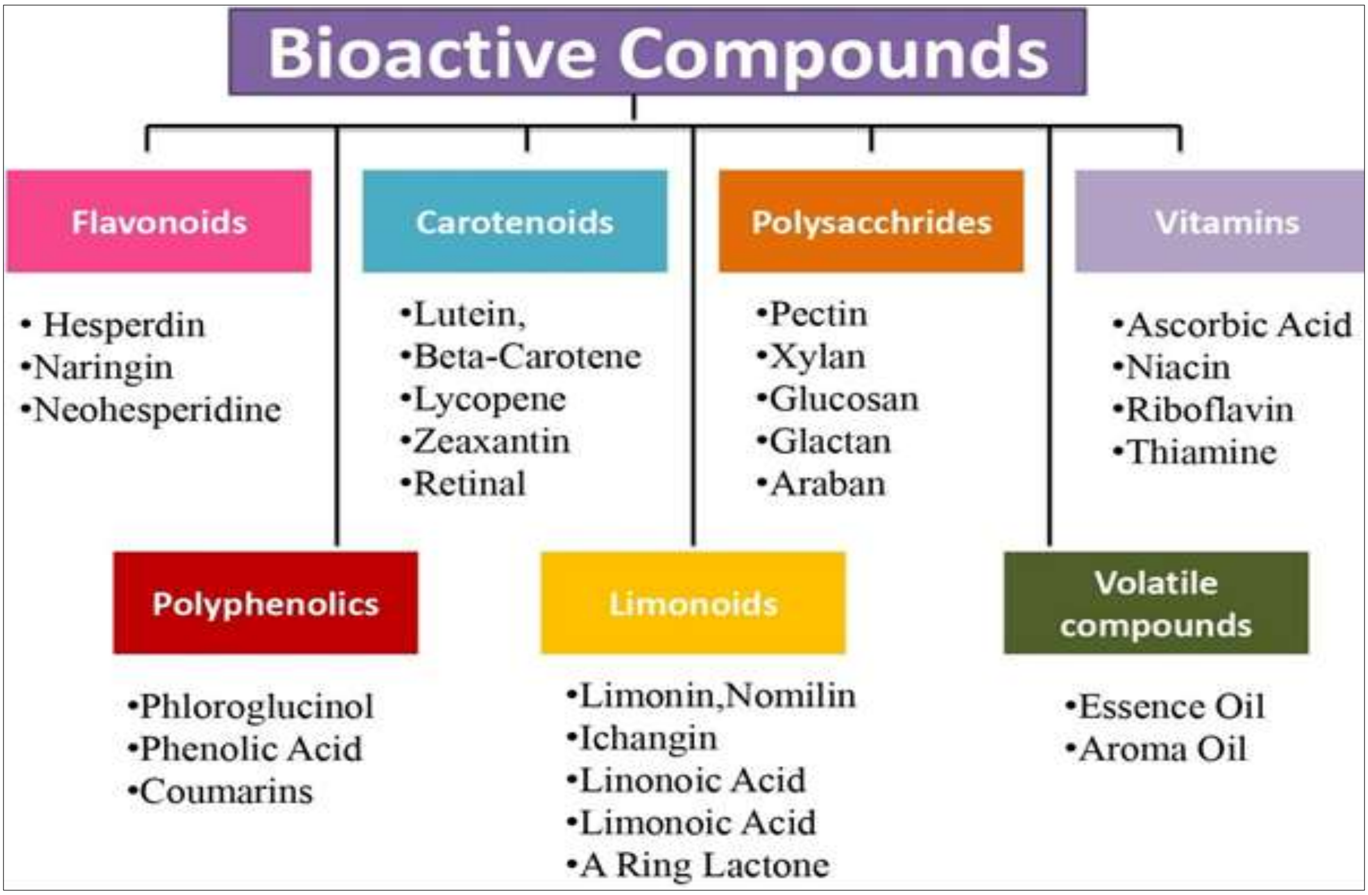

Fig 2: Bioactive compounds present in citrus peel

Flavonoids

Citrus fruits have over 60 flavonoids, which are grouped into 3 categories: flavanones, flavonols and flavones (Mahmoud *et al*., 2019) [33]. These flavonoids can be found in either glycoside or aglycone forms, but in citrus juices, they are mostly existed as flavonoid glycosides (FGs). Two kinds of di-glycosides exist in the form of glycoside of citrus flavonoids, known as neohesperidosides and rutinosides. They are l-rhamnosyld-glucosyl derivatives that are linked by interglycosidic bonds of either -1,2 or -1,6. Citrus also contains a small amount of flavones C-glycosides, where the replacement is typically on C-6 or C-8 or both position (Zaidun *et al*., 2018) [81]. Thus, flavonoids can exist in a free aglycone form, mostly exist as either C- or O-glycosides.

Flavones and Flavonols

The most prevalent flavones found in citrus peels are vicenin-2, diosmetin 6,8-di-C-glucoside, and diosmin, (Song *et al*., 2013) [49]. In lemon juice, the most abundant phenolic compounds and flavonols are rutin and myricetin, whereas quercetin and kaempferol are discovered in the peel as well as in the juice according to (Li *et al*., 2020) [85]. Additionally, in the peel, polymethoxylated flavonols, such as limocitrin 3-d-glucoside, limocitrol and iso/limocitrol 3--glucoside, are found.

Flavanones

Citrus fruits are a rich source of flavanones, which are simply reformed to isomeric chalcones under acidic or alkaline conditions (Klimek *et al*, 2020) [116]. Flavanones have a chiral center in the aglycone (C-2) and an optically active sugar residue, making them exist as diastereomers. Natural flavanones commonly hold the 2S configuration, still racemization may occur at the time of extraction (Zhang *et al*., 2019) [86]. Hesperidin and eriocitrin are abundant in citrus juice, (Smeriglio *et al*., 2018) [87]. Peel contains higher levels of flavonoids compared to the seeds. Citrus seeds have higher amounts of eriocitrin and hesperidin but very little naringin, the peel is rich in neohesperidin, neoeriocitrin, and naringin with lower levels of narirutin.

Carotenoids

Carotenoids are a widespread group of isoprenoid pigments that play important roles in photosynthesis and signaling (Saini *et al*., 2018) [88]. Carotenoids can be categorized into two major groups based on their chemical structure: (a) carotenes-the hydrocarbon carotenoids, such as α- and β-carotene, and lycopene; (b) xanthophylls-oxygenated derivatives of hydrocarbon carotenoids, such as violaxanthin, β-cryptoxanthin, lutein and neoxanthin (Saini *et al*., 2018) [88]. Xanthophylls, which contain oxygenated functional groups, can form ester bonds with fatty acids, allowing them to exist in both free and fatty acid esterified forms. On the other hand, carotenes lack oxygenated functional groups and have a simple hydrocarbon structure, which means they are only found in their free form and cannot form ester bonds with fatty acids (esterification is not possible because of the the absence of oxygenated functions groups). In citrus fruits, xanthophylls are commonly acylated with saturated and unsaturated fatty acids, including Stearate (C18:0), Palmitate (C16:0), Caprate

(C10:0), Oleate (C18:1), Palmitoleate (C16:1), Myristate (C14:0), Laurate (C12:0). In citrus, β-citraurin is produced from the CCD4b1/CitCCD4-catalyzed asymmetric cleavage (at either sides 7, 8 or 7′, 8′) of β-cryptoxanthin or zeaxanthin (Saini *et al*, 2018) [88]. The orange-red color of citrus fruits is attributed to the existence of carotenoids and apocarotenoids (Luan *et al*., 2019) [82]. The carotenoids in citrus fruits mostly comprise xanthophyll esters, which are carotenoid fatty acid esters (Etzbach *et al*., 2020). As an example, in sweet orange, the amount of carotenoids in the peel (Flavedo) at full maturity was nine times greater (12.6 mg/100 g FW) than in the pulp (1.4 mg/100 g FW).The most ample carotenoids present in the fully mature oranges' endocarp and flavedo were (all-E)- and (9Z)-violaxanthin, monoesters, and diesters esters carrying various acyl moieties such as stearate palmitoleate, caprate, laurate, oleate, palmitate, and myristate, Other significant carotenoids were (all-E)-lutein, (all-E)-antheraxanthin, and (all-E)-β-carotene. However, the study found (all-E)-lutein, (all-E)-antheraxanthin, and (all-E)-β-carotene is common in the fully mature green fruit's flavedo. Additionally, the esters of β-citraurin were also identified in the fully grown orange's flavedo. (Zacarias-Garcia *et al*., 2020) [117].

Essential Oil (Terpenes and Limonoids)

The essential oil extracted from the flavedo of citrus fruits is a valuable product because of the existence of terpenes, limonoids, carotenoids, flavonoids, and coumarins, (Raspo *et al*., 2020) [83] which have numerous beneficial health activities. The fragrance of citrus essential oil is commonly used in the perfumery pharmaceutical, food industries and cosmetics. Essential oil from citrus is also known for its antimicrobial activities potent antioxidant, anxiolytic, neuroprotective, and analgesic (Ambrosio *et al*., 2019) [84]. Citrus essential oil is recognized for its bioactive compounds with potential antimicrobial properties that induce lysis of bacterial cell walls, resulting in intracellular ingredient leakage and cell death. The potent antimicrobial effects of citrus essential oil have led to increased interest in using it as a preservation agent for vegetables, meat, processed food products and fruits. The volatile fractions of citrus essential mostly have various types of chemical constituents, including monoterpene hydrocarbons such as β-phellandrene, γ-terpinene, myrcene, D-limonene, p-cymene, β-pinene and δ-3-carene, Oxygenated monoterpenes like geranial, nonanal, and (Z)-neral, terpene alcohol such as α-terpineol, (E)-verbenol, linalool, (E)-carveol and geraniol, and sesquiterpenes such as (Z)-α-bergamotene, along with aldehydes like decanal and esters such as ethyl cinnamate and ethyl p-methoxycinnamate are also significant chemical constituents of citrus essential oil. Additionally, the non-volatile section of citrus essential oil, which makes up 1 to 15% of the cold-pressed oil, is predominantly comprised of various components such as sterols, long-chain hydrocarbons, wax, fatty acids, and limonoids (for example, limonin).

Pectin

Pectin is a composite carbohydrate that plays a vital role as an element of the primary cell wall in plants. Pectin is a polymer made up of -galacturonic acid units, and it can have different numbers of methyl ester groups. Pectin is a refined or purified carbohydrate derived from the inner part of the rind/peel of citrus fruits, mainly composed of partially methoxylated polygalacturonic acid (Oliveira *et al*., 2015) [89]. Orange peels are a significant source of pectin, which is a valuable commodity. Pectin can form gels with sugar under appropriate conditions and is frequently utilized as a natural food additive in the food industry to thicken, texturize, emulsify, stabilize, gel, and replace fat in spreads, ice cream, emulsified meat products and salad dressings (Liu *et al*., 2021) [56]. The application of pectin derived from orange peels is extensive in the food industry, as transforming orange peel into a beneficial by-product such as pectin provide great potential for utilization and simultaneously helps to reduce environmental pollution.

Table 1: Antioxidant properties of citrus fruits

Scientific Name	Citrus Fruit	Compounds	Activity	References
Citrus bergamia	Bergamot Orange	Flavonoids, (eriocitrin, neoeriocitrin, naringenin, hesperigin, neohesperidin,)Vitamins, Minerals, Pectin	Anti-Cancer, Anti-inflammatory, Protect Human Lung Epithelial Cells, Anti-infective, Anti-proliferative	A Maugeri *et al*., 2021 [40] Nadia *et al*., 2015 [90] Lombardo et al., 2020 [91]
Citrus sinensis (L.) Osbeck	Sweet Orange	Flavonoids (hesperidin, naringin); Pectin, Carotenoids, Fibre, Vitamins, Minerals, Phenolic compounds, Essential oil	Antibacterial and antifungal; anti-cancer; anti allergic; anti-obesity, antioxidant and anti- inflammatory;	Cirmi *et al*., 2020 [92] Barreca *et al*., 2016 [93] Guo *et al*.,2020 [94] Oikeh *et al*., 2020 [95]
Citrus maxima (Burm.) Merr	Pomelo	Polysaccharides; vitamin, Flavonoids (hesperidin);, Minerals, Essential oil	Antioxidant; Hypolipidemic; anti-inflammatory; hypoglycemic; anti-inflammatory; anti- cancer;	Chi *et al*., 2020 [96] Tocmo *et al*., 2020 [97] Zhao *et al*., 2019 [98]
Citrus reticulata Blanco	Mandarin Orange	Flavonoids (naringin, hesperidin, eriocitrin; quercetagetin); tannins; limonoids (limonene; β; carotenoids; phenolic compounds; vitamins; pectins, polysaccharides; Minerals	Antioxidant; anti- ulcerogenic, antibacterial; anti- inflammatory; anthelminthic anticancer; gastroprotective; antigenotoxic	Diab *et al*., 2016 [125] Hou *et al*., 2019 [72] Ishfaq *et al*., 2021 [99] Cirmi *et al*., 2020 [92] Kim *et al*., 2017 [100]
Citrus aurantiifolia	Lemon	Flavonoids (hesperidin, naringin); Vitamins, tannins; polysaccharides; Minerals	Anti-inflammatory; anti-cancer,Antioxidants	Lin *et al*., 2019 [60] Maurya *et al*., 2018 [124]
Citrus medica L.	Citron	Flavonoids; phenolic acids; vitamins; pectins; minerals	Antibacterial; antiulcer	Vahidi *et al*., 2019 [123]
Citrus paradisi	Grapefruit	Flavonoids (naringin); limonoids vitamins;	Neuroprotective ,Anticholesterolemic;	Miya *et al*., 2021 [126] *Pena et al*., 2016 [127]
		pectins; minerals (limonene; β-pinene); phenolic compounds;	prebiotic antioxidant; antitumor antibacterial	Sir Elkhatim *et al* 2019 [128] Khalil *et al*., 2020 [129]

Diseases

Fig 3: Health Benefits of Citrus Fruits

Anti – Obesity

The most well-known indications of metabolic disorders around the world are being overweight and obesity. It has been developed to numerous health issues, such as dyslipidemia, hypertension, certain cancers, and type 2 diabetes. To prevent and treat obesity, various model animal studies showed that Citrus ichangensis peel can be beneficial (Ding *et al*., 2012) [41]. Carotenoids, polyphenols (esp. tannins), vitamins, flavonoids, dietary fibers, and minerals are containing in citrus fruit which help in minimizing obesity (Edwards-Jones *et al*., 2004) [42]. 5-demethylated polymethoxyflavones (5-OH PMFs) high level are a distinctive enrichment found in Chenpi (Chenpi is dried peel of citrus fruit) (Jingjing *et al*., 2016) [131]. The impact of chenpi extract on improving metabolic characteristics was studied in a mouse model of obesity/diabetes caused by a high fat diet (HFD). Over a 15-week period, oral treatment of 0.25 and 0.5% chenpi extract in meals significantly reduced hepatic steatosis, HFD-induced obesity and symptoms of diabetes. In adipose tissue the activation of 5'-adenosine monophosphate-activated protein kinase (AMPK) is linked with positive impact (Jingjing *et al*., 2016) [131]. Citrus peel effectively reduced the increase in plasma triacylglycerol (TG) and liver lipid buildup after hexane extraction. Citrus peel dramatically increased the alpha-b (pparab), hepatic mRNA expression of peroxisome proliferator-activated receptor and its target genes, implying increased fatty acid –oxidation in the liver. Citrus peel dramatically boosted mRNA expression in visceral adipose tissue peroxisome proliferator-activated receptor gamma (Pparg) and adiponectin C1Q and collagen domains, b (Adipoqb), which are involved in development and maintenance adipose. Citrus peel has anti-obesity properties, through stimulating the hepatic enzymes PPARγ and PPARα adipocyte pathways indicates by their findings (Liqing *et al*., 2014) [132].

Anticancer

One of the most serious diseases threatening human health is Cancer, encompassing over 100 types of abnormal cell division that are uncontrollable with metastatic features (Pugazhenthiran *et al*., 2021) [45]. Citrus peel bioactive components have been shown to have clear inhibitory effects on tumor growth (Miwa *et al*., 2005) [46]. Recently, epidemiological studies depicted that there is a direction relation that the consumption of flavonoids may reduce the risk of developing colon cancer (Andrews, 2013 and La-Vecchia *et al*., 2013) [47-48]. Moreover, with high intake of citrus fruits help women get out of the risk of gastric cancer and breast cancer with 10% reduction (Song and Bae, 2013) [49]. Essential oil, d-limonene are the most abundant ingredient that has been found to have anti-proliferative and apoptosis-inducing actions found in navel orange hence it act as a chemotherapeutic and chemo preventive agent against various malignancies. Pinene an essential oil component has been demonstrated to suppress the development of cancer in lungs cells. By suppressing the cancer stem cell marker ALDH1A3 (Aldehyde dehydrogenase 1 family, member A3) citral might diminish MDA-MB-231 cell growth, which revealed that NOEO may also have anticancer effects (Yang *et al*., 2017) [50].

Anti- inflammatory

Citrus peels have strong anti-inflammatory properties because they decrease gene expression and enzymes involved in inflammation (Huang and Ho, 2010) [51]. Moreover, inflammation may reduced by PMF-mediated calcium-signaling-induced apoptosis. PMFs are found only in mandarin oranges (Citrus reticulate) and sweet oranges (Citrus sinensis) peel whereas Flavonoids are distributed through the whole fruit. The most abundant PMFs such as tangerine and nobiletin is found in orange peel extract (OPE). It have been shown to have substantial anti-inflammatory effects that can inhibit, COX-2, iNOS, IL-6, IL-1, TNF-, 15-LOX, PLA2 and NADPH oxidase in several animal models and cell-based (Alexander Gosslau *et al*., 2014) [52]. Citrus fruit peels' inhibitory action on PGE2 synthesis was attributed to polymethoxy flavones, particularly nobiletin found in citrus peel (Yung-Sheng *et al*., 2009) [130]. Moreover, the hydrophobic property of polymethoxy flavones allows them easily to pass the intestinal barrier, allowing them to be absorbed more rapidly into the human body. Polymethoxy flavones are more anti-inflammatory than flavanone glycosides and appear to be potential therapeutic phytochemicals of citrus by-products (Li *et al*., 2006) [53].

Anti- asthma

Since ancient times in China dried citrus peels used as an active anti-asthmatic therapy had been recorded. With new studies, the alkaloid component has anti-asthmatic capabilities in dried citrus peels. Synephrine and N-methyl tyramine are the major alkaloid components of citrus peels. Synephrine (0.3829%) is the most source of alkaloid in dried citrus peels, having the capacity to increase hypertension, expand the trachea, constrict blood vessels, calorie intake as well as boost metabolism (Yu *et al*., 2018) [55]. Nobiletin was shown to lower eotaxin levels in an *in vivo* studies, it reduces airway inflammation and eosinophil infiltration in asthmatic rats by an efficient eosinophil chemoattractant cytokine (Liu *et al*., 2021) [56].

Anti Hyper-lipidemia and Hypo-lipidemia

Red-orange and lemon extract (RLE) was made by well combination of anthocyanins and other polyphenols recovered from red-orange processing waste with eriocitrin and other flavanones that are from citrus peel using a patented extraction procedure. *In vivo* experiments RLE was used to test for a potential beneficial effect on the metabolism of lipids and glucose. Experiments on male CD1 mice fed a high-fat diet has found that an 8-week treatment with RLE could result in a significant decrease in triglyceride levels, blood cholesterol, and glucose, which has a favourable influence on hyperglycemia control and lipid metabolism, indicating that this novel phyto-extract could be used in nutraceuticals. The responses to dietary supplements containing citrus PMFs in people with moderate hypercholesterolemia and baseline traits associated with metabolic syndrome in human studies revealed that a four-week period improved blood lipid profiles without creating any negative repercussions. Lipid-lowering effects were observed earlier, in hypercholesterolemic patients who consumed orange juice for one month (four weeks). In mildly hypercholesterolemic males, combinations of tangerine and nobiletin at 270 mg/day, along with tocotrienols (30 mg/day), lowered Apo-B, triglycerides and LDL-C in plasma (Roza *et al*., 2007) [58]. Citrus polymethoxylated flavones (PMFs), such as naringin, citrus flavanone glucosides or, tangeretin, and hesperidin were tested for cholesterol-decreasing ability and triacylglycerol levels in hamsters with diet-induced hypercholesterolemia. (Korowska *et al*., 2004; 2001) [59]. Citrus fruit has strong DPPH and ABTS free radical scavenging activity, making it an excellent lipid peroxidation inhibitor. To combat hyperlipidemia, citrus fruit was discovered to lower LDL (Lin *et al*., 2019) [60]. Hesperidin consumption affects lipid metabolism by reducing cholesterol levels in the blood, as well as anti-hyperglycemia and hypolipidemic reactions (Rekha *et al*., 2019) [61].

Anti – Diabetes

For the twenty-first century's one of the epidemics, that has been increasingly limiting the quality of the people's life is Type 2 diabetes (T2D). Reports on the consequences of certain fruits and vegetable have been identified as the prevention and treatment of T2D (Arulselvan *et al*., 2014; Gugliucci *et al*., 2009) [62-63]. Hesperidin has an impact on insulin and glucose metabolism. The fundamental pathogenic event in diabetes mellitus is a disruption in blood glucose control. Hesperidin has been found in studies to lower glucose and fat levels by activating glucose-regulating enzymes. The reduce glucose uptake, inhibiting intestinal and renal sodium-glucose co-transporters of naringenin in Citrus phytophenolics' mechanisms of action in diabetes models has been suggested (Li *et al*., 2006) [53] (and glucokinase mRNA levels has been found to be increased by both naringenin and hesperidin significantly, while naringeinin decreased phosphor phenolpyruvate carboxykinase and glucose-6-phosphatase mRNA expression in the spleen (Jung *et al*., 2006) [65]. Many studies showed that citrus peel extract are able to lowered the adipocytokines induced by the high-fat diet (leptin and resistin), as well as increasing the phosphorylation of protein kinase AMP-activated (AMPK) in muscle tissues, stimulating the activity of transcription of the peroxisome proliferator-activated receptor gamma (PPAR-) gene which is in a manner of dose-dependent (Balwinder Singh *et al*., 2020) [66].

Table 2: Uses of Bioactive compounds to treat diseases

Compounds	Disease Treatment	Activity	Reference
Naringin	Anticancer metastasis Cell cycle arrest	Metallopeptidase-9 (MMP-9) is used for suppression of upregulation and PI3K/AKT/mTOR/p70S6K is repressed for signaling pathway G1 cycle arrest by increasing p21 and decreasing surviving in MDA-MB-231 xenograft mice.	Ye *et al*., 2012 [101] Charoensinphon *et al*., 2013 [67]
Hesperetin	Suppress proliferation Cell cycle arrest Anti-diabetes effect	1, 2-dimethylhydrazine which effect the Inhibitory on proliferating cell nuclear antigen in ACF exerting Colon Cancer Model in rats. In Ovariectomized athymic mice, the growth of aromatase-expressing MCF-7 tumor is greatly reduced in CDK4, Bcl-x(L) and cyclin D1, while p57 levels are upregulated. In human breast cancer MCF-7 cells by downregulating CDK2 and CDK4 together with cyclin D in the G1 phase cell cycle arrest and also upregulating p27Kip1 and p21Cip1. Induced the G2/M phase and increased expression of caspase-8, caspase-9, caspase-3, Bax, p53, and Fas death receptor and its adaptor protein Fas-associated death domain-containing protein (FADD) in human cervical cancer SiHa cells. Hyperlipidemia and Hyperglycemia is reduced forcefully by Hesperidin aside normalising hepatic glucose-regulating enzyme activities and decreasing blood glucose, bone metabolic and bone tissue parameters are not affected in Streptozotocin (STZ), when injected to marginal diabetic weanling rats.	Lai *et al*., 2013 [102]; Vermeulen *et al*., 2003 [103]; Park *et al*., 2012 [104] Akiyama S. *et al*., 2010 [105]
Nobiletin	Antiangiogenesis Cell cycle arrest Improves the cognition of patients with Alzheimer's disease.	Angiogenic differentiation caused by FGF and VEGF is inhibited by downregulation of c-JNK and ERK1/2 also in the Caspase pathway activation. Cell cycle progression is blocked at G1 breast cycle cell lines such as MCF-7, MDA-MB-435 and human colon cancer line HT-29. Increased in Hepatic and Peripheral insulin sensitivity, Improved Glucose Tolerance and Protected against development of Atherosclerosis in Liver by regulating Nobiletin.	Wang *et al*., 2014 [70] Alshatwi *et al*., 2013 [69] Gopalsamy *et al*., 2020 [106]
Tangeretin	Suppress proliferation Anticancer metastasis Scavenging of ROS	Caspase-3 activation and surface phosphatidylserine is elevated in human cocon LoVo/Dx cells. Migration of Aortic smooth muscle cells and PGDF-BB-induced proliferation is inhibited by blocking AKT activation. By the help of CAT, GPx, SOD and nonenzymatic antioxidants inhibits phase II detoxification in 7, 12-dimethyl benz(a)anthracene and cancer cell proliferation induced mammary carcinoma in rats.	Wang *et al*., 2014 [70]
Sinensetin	Antiangiogenesis	Angiogenesis is inhibited by inducing Cell Cycle Arrest(CCA) in G0/G1 phase in Human Umbilical Vein Endothelial Cells (HUVEC) culture; Angiogenesis genes such as hras, flt1 and Kdrl which are the expressions of mRNA is down regulated in Zebra fish embryos	A. Ahmadi *et al*., 2008 [107]

Potential Industrial Application
Animal feed
Orange peel is a vast source of nutrients for microbial communities, particularly those found in the rumen, which have altered to use plant material. This property has been utilized by feeding high-energy orange waste to ruminants to promote lactation and microbial growth. Bampidis and Robinson (2006) [22] reported that cattle fed with orange waste gained more weight compared to those fed with starch-rich feeds. Tripodo *et al*. (2004) [108] developed a method to produce animal feed from centrifugation pulp of citrus juice by subjecting it to alkaline or enzymatic treatments. Although the protein content was not high, it was comparable to other agro-industrial waste products and had good digestibility. However, the addition of orange peel to the feed is limited because it can cause rumen parakeratosis, especially if forage consumption is low (Prasad *et al*., 2018) [109].

Organic fertilizer
One potential use of orange peel waste is to create organic fertilizer through composting techniques (Heerden *et al*., 2002) [118]. This process involves modification of the citrus peel waste by changing its (Carbon/Nitrogen) ratio, moisture and pH content to 24:1,60% and 6.3and piling the altered substrate under shelter. One potential use of orange peel waste is to create organic fertilizer through composting techniques. With regular turning and watering, the composting process can be completed within three months (65 to 70 days). Although the high conductivity of the compost can promote the compost's air-filled porosity, bulk density, water holding capacity and salinity are typically within the limits that promote the growth of plant. In field experiments, preplant incorporation of the compost within the soil at different rates (2, 4, and 8 kg/m2) which improved the growth of citrus trees up to 25%, compared to control groups planted in non-amended soil. In addition, the ability of orange peel waste as an organic fertilizer was also considered by testing its effect on lettuce yields. The study found that drying and grinding the citrus peel to a regular size of 10 mm and then adding it to the soil to increase its nitrogen content improved lettuce yields (Lactuca sativa L. osteolata variety) in poor soil (Jose *et al*, 2010) [119].

Bio-refinery of orange peel
The use of orange peel in its direct form is an easy and cost-effective solution that can greatly enhance the utility of this waste material. Orange peel consist of various valuable compounds that can be further extracted and utilized by adopting a biorefinery approaches. A biorefinery is a efficiency that employs different biomass conversion processes and equipment to power, produce fuels and chemicals from waste biomass (Wikandari, *et al*., 2019) [110]. This approach is similar to the way petroleum refineries operate by producing multiple products from crude oil. The current practice of treating most of the remaining plant as low-grade waste, after harvesting the high-value grains from crops such as cereals, differs from the biorefinery concept. By extracting different number of

products, a biorefinery can make use of the various biomass components and intermediates, thereby maximizing the value obtained from the biomass feedstock and minimizing waste. Citrus fruits contain essential oils that are broadly used as flavours in food industry. These oils are present in oil sacs or glands of the flavedo, the outer part of the citrus fruit, and range in diameter from 0.4 to 0.6 mm. Orange peel, in particular, has more than 5 kg of oil per 1000 kg of oranges, and approximately 90% of this is D-limonene, a cyclic terpene characterized as a hydrocarbon (Alisaraei *et al*., 2017) [122]. D-limonene is a colorless liquid with an intense orange odor and is the important constituent of the citrus family (Rutaceae). It is commonly used as a flavouring agent in the production of food and medicines and has multiple applications in the cosmetics, chemical industry and household products. D-limonene can be extracted from orange peel using different methods such as steam distillation, solvent extraction using hexane or carbon dioxide or cold pressing (Volpea *et al*., 2015) [120]. The extraction process is well-established and relatively simple.

Ethanol
Orange peel has shown potential as a source for ethanol production using Saccharomyces cerevisiae, (Wilkins *et al*., 2007) [26] which is more efficient at transforming orange peel to ethanol than Kluvyeromyces marxianus. However, the high concentration of organic acids and essential oils are known to have antimicrobial properties, in orange peel can inhibit ethanol production. To overcome this, it is important to provide the concentration of D-limonene, the main essential oil in orange peel, which can prevent ethanol production. Researchers have found that the least possible inhibitory peel oil concentrations production of ethanol are 0.05% at 24 h, 0.10% at 48 h, and 0.15% at 72 h for both S. cerevisiae and K. marxianus (Wilkins *et al*., 2007) [26]. Pre-treatment by steam exposure can remove up to 90% of D-limonene in the orange peel, and pH neutralization is needed to attain maximum productivity as organic acids become less toxic to open or bare microbial cells.

Industrial enzymes
In food industries, pectin enzymes are often used to extract and clarify fruit juices, and citrus peels are a good source of pectin that can activate the synthesis of pectic enzymes by microbial communities that grow on them (Sulieman *et al*., 2013) [114]. A laboratory-scale study showed that pectin enzyme production by Aspergillus foetidus using citrus waste as a substrate resulted in high viscosimetric activities upto 1600-1700U/g after 36 hours of culturing, and the yield of pectinases was 25% higher than that obtained with apple pomace as the substrate under the similar parameters (Farahnaky *et al*., 2005). Other studies looked into pectinase production by various fungi, including Penicillium charlessi, Talaromyces flavus and Tubercularia vulgaris, in solid-state cultures on citrus pulp waste. P. charlessi generated highly active pectic enzymes between 4 and 6 days of cultivation (15.06 U/g DM), followed by T. vulgaris (14.04 U/g DM) and T. flavus (9.42 U/g DM). The production of multienzyme preparations having cellulolytic, pectinolytic, and xylanolytic enzymes by mesophilic fungi, Penicillium decumbens, Aspergillus niger BTL, Neurospora crassa DSM 1129, Fusarium oxysporum F3, was also investigated under solid-state fermentation using dry orange peel as the substrate, and it was found that aletring the initial pH and moisture conent improved enzyme production (Mamma *et al*., 2008) [111].

Single cell protein
In the food industry, single cell protein (SCP) obtained from cultured microorganisms such as algae, bacteria or yeasts is often used as a substitute for protein-rich foods, particularly in pet food. Waste of orange peel can also be utilized as a substrate to extract Single cell protein. Geotrichum candidum grown on acid-pretreated orange peel in solid-state cultures has been shown to produce SCP with a crude protein content of 35-40%, which has immense high *in vitro* digestibility ranging from 73-88%. Additionally, by recovering the solid residue left after the acidic pre-treatment of the peel, a high-value by-product, hesperidin (also known as vitamin P), was obtained with yields that ranges from 3.7% and 4.5% DM (Jose *et al*., 2010) [119].

Activated citrus peel extract
Orange peel can also be utilized as an activated citrus peel extract (ACPE), which is composed of different components such as flavonoid glycosides oligosaccharides, triglycerides, short peptides and fatty acids (Medvedev and Kat, 2004) [30]. ACPE has demonstrated its efficacy as a treatment for skin ailments and is suitable for use in preserving various products, including food, beverages, and cosmetics.

Paper pulp supplement
Orange peel shows great potential as a viable option for the addition of paper pulp supplements due to its high cellulose and hemicellulose content, as well as its low lignin and ash concentrations, as demonstrated by previous research (Ververis *et al*., 2007) [112]. In fact, adding orange peel to paper pulp has been shown to increase bursting strength and decrease tearing resistance without negatively impacting breaking length. Additionally, the price of orange peel is less than that of conventional pulp, resulting in a reduction in final paper price of 0.9-4.5% (Kasaai *et al*., 2017) [113].

Preparation of citrus peel packaging films
Researchers are increasingly concerned about the environmental impact of non-degradable petroleum-based polyester, which has led to a growing interest in developing biodegradable plastic materials. One such material that has been investigated is a plastic made from citrus peel, developed by researchers at Cornell University in New York. The process involved oxidizing orange peel oil to obtain limonene oxide, which was combined with carbon dioxide to create a novel polymer. This new polymer was found to have similar characteristics to polystyrene, but with greater flexibility and biodegradability. The polymer also helped to lock carbon dioxide in the atmosphere, which is otherwise considered an environmentally harmful greenhouse gas. Arrieta *et al*. (2013) [121] developed a food packaging film with these properties.

Various extraction techniques of bioactive compound from citric peel
Citrus is known for its nutrient content and its ability to promote health. Zou, Z *et al*. (2016) [7] mostly terpenoids (limonoids and carotenoids), pectin, and phenolic compounds (coumarins, flavonoids, and phenolic acids) (Saini *et al*., 2022) [8]. Citrus fruits are rich in minerals and nutrients, such as tocopherols, ascorbic acid (vitamin C), and tocotrienols

(vitamin E) (manganese, iron, selenium, copper, and zinc). Zou *et al*., (2016) [2]; Saini *et al*., (2022) [8]. It is vital to develop a standardized and integrated approach to screening out bioactive compounds that provide benefits for human health in light of the wide variances among bioactive compounds and the abundance of plant species. Azmir *et al*. (2013) [2] reported Bioactive chemicals could only be further separated, identified, and characterized before going through the proper extraction method. To understand the selectivity of extraction from various natural sources, several extraction techniques should be employed in various conditions. The extraction of bioactive substances is also possible using various methods, many of which have remained unchanged for hundreds of years. Each of these techniques has the following objectives in common: (a) to isolate specific biologically active components from complex plant samples; (b) to improve quantitative methods selectivity; (c) to boost the responsiveness of bioassays by boosting the amount of the targeted compounds; (d) to transform the bioactive components into a form that's also particularly suited to identification and isolation; and (e) to offer a reliable technique that is unchanged by modifications in the sample. There are different extraction techniques, *viz*., high-pressure assisted extraction (HPE), ultrasound-assisted extraction (UAE), enzyme-assisted extraction (EAE), and microwave-assisted extraction (MAE). (M'hiri *et al*., 2014) [3].

Microwave-assisted extraction (MAE)

Microwaves are non-ionizing electromagnetic (EM) waves with frequencies ranging from 300 MHz to 300 GHz. While 2,450 MHz frequency is frequently used in home microwave ovens, 915 MHz frequency is regarded as more advantageous for industrial applications due to its larger depth of penetration (Winny Routary and Valeria Orsat, 2012).

Using a microwave and aqueous ethanol, it was possible to extract 5.86 g/100 g of hesperidin and 1.31 g/100 g of narirutin from mandarin peels. Additionally, total polyphenols of 131.57 mg/100 g and total flavonoids of 637.59 mg QE/100 g were present in the aqueous methanol extract of orange peels. The TPC content increased as the microwave power was increased from 400 to 500 W, but there was a substantial reduction in TPC with each subsequent increase in microwave power, with the lowest value at 800 W. The breakdown of polyphenols at higher microwave energy may be the cause of this effect (Kaur *et al*., 2023) [12].

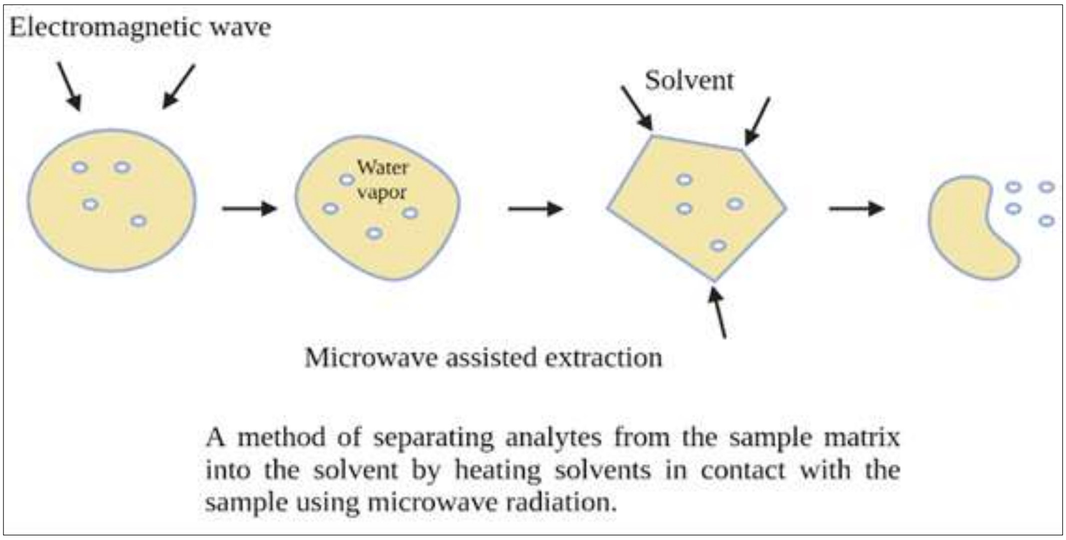

Fig 4: Microwave-assisted extraction

5.2. Ultrasound-assisted extraction (UAE)

Ultrasound waves with a frequency range of more than 20 kHz and a sound intensity of 5–1000 W/cm2 are used during the ultrasound-assisted extraction (UAE) operation. UAE has evolved into a process that makes sure it satisfies the requirements as an economical, cutting-edge extraction method. From natural plant sources and their by-products, several biomaterials and macromolecules have been extracted utilizing ultrasonic technology (Rifna *et al*., 2021) [5].

The separation of flavonoids from citrus peels were investigated by Putnik *et al*. (2017) [17], utilizing the UAE (lime, orange, and tangerine). Lime, orange, and tangerine each had a total phenolic content in the flavonoid fractions of 74.801.90, 66.360.75, and 58.684.01 mg GAE (gallic acid equivalents)/g, respectively (Citrus tangerine). The most difficult source was orange peel, which contains hesperidin, diosmin, nobiletin, neohesperidin, and tangeritin. The tangerine peel, which solely contained hesperidin and neohesperidin, was the most straightforward source. The antioxidant activity of each component of the flavonoid fraction varied, and both the total phenolic content and yields from dry material were higher than those from wet material (p 0.01). The length of the extraction process had no effect on the phenolic content over the course of the research. A frequency of 60 kHz, a 30-minute extraction period, a temperature of 40 °C, a citrus peel/water ratio (g/mL) of 1/10, the use of Ca (OH)2 as the basifying agent, and water as the solvent produced the best results for UAE. Under these circumstances, the yield was 40.25 12.09 mg/g (4.025 1.209% DM), while the total phenolic content of the peel dry matter was 19.595 2.114 mg GAE/g.

Ultrasound improved the trans-b-carotene extraction from orange peels. The trans-b-carotene extraction yield was shown to rise as particle size decreased (down to 0.28 mm); however, when trans-b-carotene was extracted from extremely fine powders, no meaningful gain in yield was found because the cell walls had already been broken during the process of fine grinding. Due to the combined effects of cavitation and heat treatment, the extraction yields increased with ultrasonication intensity when the temperature rose from 25 C to 45 C. The effects of temperature, extraction duration, and amplitude (at 20 kHz) on the extraction of carotenoids by ultrasonication are significant. "GRAS" solvents like ethanol may be used to extract carotenoids more successfully. Lutein content was found to be at its highest level at 43 C, 34 min of extraction time, and a 33% amplitude (Kaur *et al*., 2023) [12].

Gavahian *et al*. (2019) [13] compared the results to those of phenolic compounds recovered through maceration from the dried peels of mandarin oranges (*Citrus reticulata*) using the response surface approach for the UAE. Their research revealed that extraction time, temperature, and input power can have a substantial impact on a number of variables, including extraction yield and total phenolic content. The maximum oil concentration (27%) and phenolic content (15 263 mg Eq gallic per 100 g DW) were obtained by operating the UAE for 40 minutes at 57 W of power and 48 °C of temperature, and this can be regarded as the ideal extraction setting. Equipment for ultrasonic-assisted extraction is shown schematically in the figure.

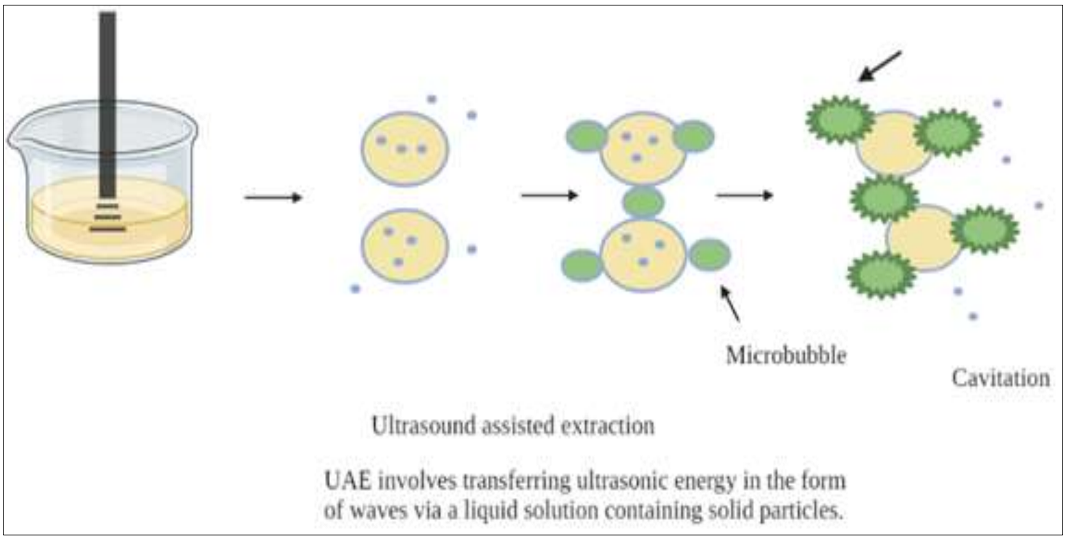

Fig 5: Ultrasound-assisted extraction

Enzyme-assisted extraction (EAE)

Using enzymes to remove citrus byproducts significantly improves the recovery of phenolic chemicals. With a rise in enzyme concentration, antioxidant, and polyphenol extraction yields increased significantly. First, b-glucosidase (at 20 U/g) was applied to citrus pomace for 24 hours to obtain extracts rich in bioactive substances, including hesperetin and naringenin. Hesperetin and naringenin content significantly decreased after 24 hours, which may have been caused by the chemicals' oxidation or hydrolysis degradation. Using pectinase and cellulase to extract polyphenols from citrus peels, research reported that yields in albedo improved by more than 60% while recovery of polyphenols in flavonoids increased by about 30% (Kaur *et al*., 2023) [12].

Flavanones formed 3.4% of the total polyphenol content (TPC) after being extracted from citrus pomace using EAE. This extract was high in aglycones (naringenin and hesperetin). By analyzing their effects on the pathogenic activity and adhesion of this pathogen, this research helped to understand the functional potential of glycosylated flavanones and aglycones for inhibiting the attack, adhesion, and proliferation of S. Typhimurium in the abdomen. (Kaur, S. *et al*., 2023) [12]. Enzyme-assisted extraction is illustrated in the figure.

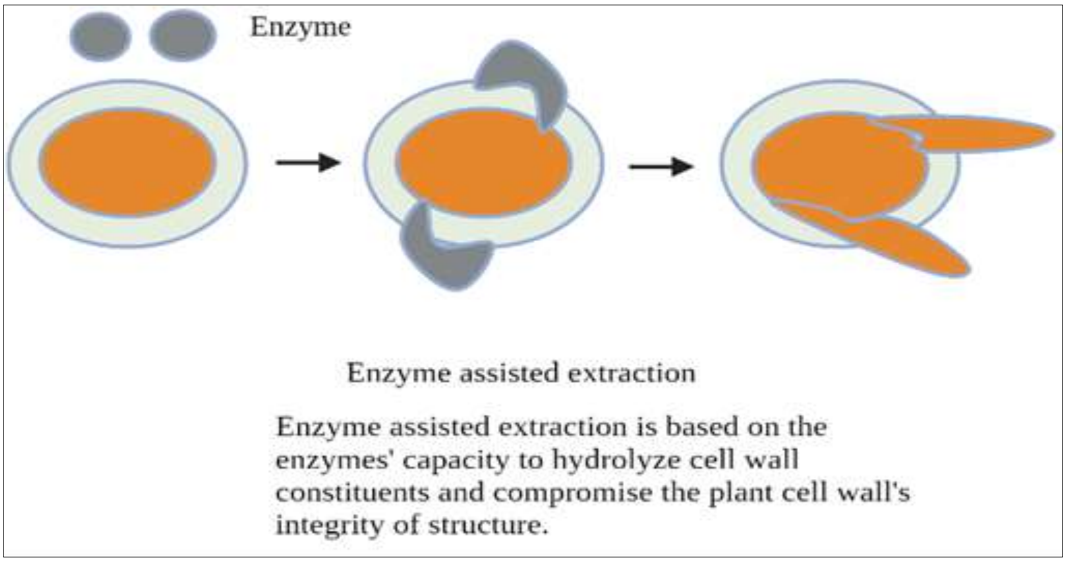

Fig 6: Enzyme Assisted Extraction

High pressure assisted extraction (HPE)

It is a new, non-thermal process that results in foods with higher aspects, increased safety, and a longer life span. The loss of a food's nutritional content and texture is negligible due to high-pressure processing's less impact on the covalent bonds of low-molecular-mass, such as flavor and color. To eliminate the dangerous bacteria that contaminate food, high-pressure processing normally uses pressure ranging from 300 to 700 MPa. Varying temperature and pressure configurations can also provide desirable qualities including texture, flavor, and color (Pathaw *et al*., 2020) [14].

Two studies have documented the effects of citrus peels' antibacterial and antioxidant properties, as well as the effects of HPE (3–10 min, 300–500 MPa) (lemon, sweet orange). In comparison to the control samples, HPE (10 min, 300 MPa; 3 min, 500 MPa) produced higher polyphenol extraction yields from lemon and orange peels. Orange peel extracts had a much higher polyphenol concentration than lemon peel extracts, with the exception of 500 MPa. This is explained by the various levels of sensitivity to high pressure that the tissues of orange and lemon peels exhibit. However, antioxidant activity and phenolic content (measured by DPPH) both for lemon and orange peels decreased under more demanding HPE conditions (500 MPa, 10 min). However, it was discovered that HPE at 300 MPa for 3 minutes produced the maximum polyphenol output from orange peel Putnik *et al*., (2017) [17]. Moreover, strong antimicrobial activity has been shown by the extracted orange peel against both gram-negative and gram-positive bacteria, including Listeria innocua and Acinetobacter (Putnik *et al*., 2017) [17]. A diagrammatic representation of high-pressure assisted extraction is given in the figure.

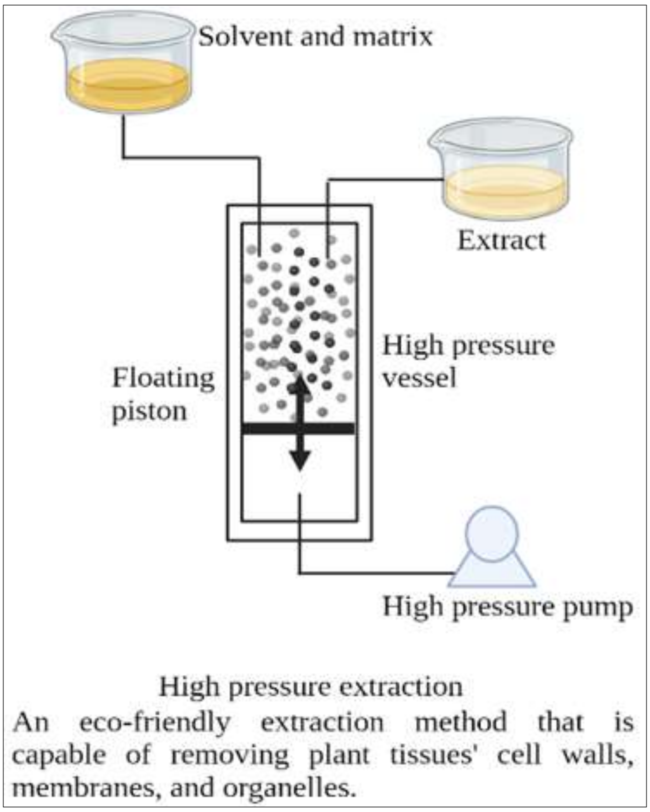

Fig 7: High pressure assisted extraction

Table 3: Combination of non – thermal techniques in extraction for the recovery of bioactive compounds from different fruit peel.

SL No.	Name of the by-product	Combination of extraction processes	Optimized condition	Bioactive compounds	References
1	Citrus sinensis (Orange) peel	PEFE+EAE	The viscozyme used for the enzymatic hydrolysis had a high voltage energy input of 222 kJ/kg.	Reducing sugars, Polyphenols	(Patra *et al*. 2022) [139]
2	Citrus limon (Lemon) peel	PEFE+SFE	The temperature is 35 C, the co-solvent flow-rate is 1ml/min, and the pressure is 162.12 bar.	Polyphenols, Eriocitrin	(Kaur *et al*. 2021) [141]
3	*Citrus reticulata* (Mandarin) peel	UAE+CEM	The working frequency of an ultrasonic processor, which was set at 20 kHz, 50% aqueous ethanol.	Carotenoids, Flavonoids	(Anticona *et al*. 2021) [140]
4	Citrus paradisi (Grapefruit) peel	SFE+PEFE	Pressure is 305 bar, CO_2 flowrate is 35g/min and temperature is 70 C.	Lycopene, Naringin	(Kaur *et al*. 2021) [141]
5	Citrus aurantiifolia (Lime) peel	MAE+UAE	Ultrasonic energy of 38% amplitude for 4 minutes while using 140 W of microwave power and 55% ethanol.	Phenolic compounds, Antioxidants	(Patra *et al*. 2022) [139]

MAE = Microwave assisted extraction
UAE = Ultrasound assisted extraction
EAE = Enzyme assisted extraction
PEFE = Pulsed electric field extraction
SFE = Supercritical fluid extraction
CEM = Control extraction method.

Future Perspective

As consumers become more conscious of a balanced diet and diet-related health issues, plant-based food or functional food is highly emerging in the market. The increasing demand for natural ingredients has spurred the search for newer, more affordable plant-derived nutraceuticals that may eventually replace pricey synthetic food supplements. This calls for interdisciplinary research that may include, among other fields, food chemistry, food technology, biotechnology, medicine, molecular biology, and toxicology. There are several challenges that must be surmounted in order to assess the potential of citrus-derived nutraceuticals. To begin with, sufficient infrastructure and treatment facilities are required, especially in developing countries where there aren't enough facilities for waste management and safe disposal, to handle the enormous amounts of citrus wastes that are mounting on the outside processing industries around the world. To generate value-added products and justify investments, it is essential to carefully collect waste materials and thoroughly segregate them rather than processing all of the garbage at once. For instance, the most important phenolic chemicals to use in the food and pharmaceutical sectors are tannins, phenolic acids, and flavonoids. It is crucial to carry out additional analyses to ascertain the makeup and concentrations of bioactive compounds before adding them as food additives. (Gao *et al*., 2020) [133].

In order to maximise the economic potential of the businesses that process citrus waste and support the initial investment, it's also critical to develop a working policy that incorporates many different stakeholders, including investors, associations of those with an interest, and potential end users. It is crucial to remember that excessive diet modification can occasionally have deadly consequences. This subject needs to be further investigated to avoid posing any health risks to customers. The complete protocol must be evaluated, standardized, and the subject of scientific study for the consumer to accept it. Additionally, the developed nutraceuticals and pharmaceuticals' efficacy and safety through testing on humans and animals for purported health benefits (Mahato *et al*., 2018) [134].

Conclusion

It was concluded that citrus peels extracts are potential sources of natural antioxidants. All the extraction techniques showed free radical scavenging activities. It is concluded from the study that microwave assisted extraction technique is more effective. The main attention given here is to the extaction for the best results and best use of the waste. A citrus peel contains important bioactive compounds which can be used to form a value added product. The amount of bioactive compounds are different depending on the technique used. Generally speaking, microwave-assisted extraction techniques are superior to or on level with traditional solvent extraction techniques. Extraction efficiencies can be greatly increased by using modern technologies and process parameter optimisation. Therefore, there is still much to learn about extraction methods as well as technology in order to enhance the extraction of flavonoids.

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