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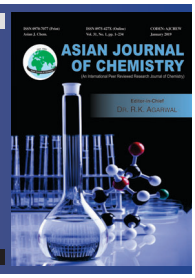

REVIEW

Citrus Peel as a Source of Beneficial Phytochemical and Pharmacological Potential

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Citrus fruits are produced industrially and globally cultivated for many functions due to having beneficial bioactive compounds including phenolic and flavonoids. However, the increasing number of productions contributes to increasing agricultural waste which causes environmental problems and the disposal results in high economic costs. Peel is one of the major sources of this waste. These citrus by-products, which are generally discarded as waste, has promising potential in nutraceutical resources. The methods employed in this review are *via* comprehensive bibliographic metadata base (PubMed, Google Scholar, Scopus, *etc*.). Citrus and citrus peels contain common polyphenols such as citrus flavonoids, hesperidin, narigin, nobilentin, tangeretin, neohesperidin, narirutin, eriocitrin, didymin and rutin among others. These compounds displayed diverse pharmacological activity such as anticancer, antidiarrheal, antihypocholesterolemic, antiobesity, antidiabetic, antioxidant, anti-inflammatory and antiosteoporosis properties. This review is on the phytochemical and pharmacological properties of citrus peel and the literature are based on previous researches' studies and reports. However, further investigation on the possible underlying mechanisms and their efficacy as medicine is still in need to be further explored.

Keywords: Citrus peels, Pharmacological, Phytochemicals property.

INTRODUCTION

Citrus plant is native to tropical Asia. Despite that it is also found in all tropical and subtropical country. The world-wide annual production of citrus fruits is 105 million metric tons between 2000 and 2004 [1] and has been increasing steadily throughout 2000s reaching over 124 million tonnes by 2016 [2]. Citrus fruits belong to the family Rutaceae of the genus Citrus. Which includes fruits such as tangerine, orange, lemon, lime and grapefruit. Citrus fruits are well-known as a source of beneficial nutrients as well as phenolic compounds which are for human health. In major citrus producing countries such as Brazil and the United States, the percentage of fruits being utilized into juices reaches 96 % while the average percentage is 34 % [1]. Based on the average yield of juices, peel of citrus covers a big part of surplus [1,3-5]. Owing to a large amount of waste produced, fermentation of the waste is affecting the environment. Citrus by-products which eventually discarded as waste to environment, can potentially be a resource for food processing and nutraceutical [6]. Citrus peel is the rind or skin, as the outer protective layer of the fruit which can be peeled off. The thick part of the citrus peel is called a hesperidium. In hesperidium, the inner layer (also called albedo or, among non-botanists, pith) is peeled off together with the outer layer (called flavedo) and together they are called the peel. The flavedo and albedo are the exocarp and mesocarp, respectively. The juicy layer inside the peel (containing the seeds) is the endocarp. Peel has an interesting source of phenolic compounds, which include phenolic acids and flavonoids. Flavonoids are represented in citrus fruits by two very peculiar classes of compounds: polymethoxylated flavones and glycosylated flavanones. They are exclusively found only in citrus fruits, and their pattern is specific of each species, which makes them very good markers of adulteration in commercial juices [7-9]. The citrus flavonoids have been found to have health-related properties, which include anticancer, anti-inflammatory activities, antihypocholestero-

lemic, antidiarrheal, antidiabetic, antiobesity and antiosteoporosis. The purpose of this review is to do an overview on phytochemical and pharmacological potential of citrus peel towards benefiting health view by previous researchers.

A comprehensive bibliographic research was conducted to give an in-depth insight into the phytochemical and pharmacological properties of citrus peel. The authors carried out a literature review by means of the scientific engine, Google Scholar (http://scholar.google.com) and *via* databases PubMed (http://www.ncbi.nlm.gov/pubmed), Scopus (http://www.scopus.com), Sciencedirect (http://www.sciendiect.com), Elsevier (http://www.elsevier.com), Researchgate (htpps://www.researchgate.net), American Association for Cancer Research (cancerres.aacrJ.s.org), Emeraldinsight (www.emeraldinsight.com) and Google Books (https://books.google.com). This review is the study on phytochemical and pharmacological properties previously reported on citrus peel by researchers around the globe.

Morphological description of citrus peel: Citrus peels are comprised of two regions, the flavedo and albedo (Fig. 1). The flavedo consists of characteristic peel oils and pigments while albedo is the white pithy region [10]. The citrus fruit is a hesperidium, a berry with a leathery rind. The endocarp (flesh) has separate sections (carpels) filled with fluid-filled sacs (vesicles) that are specialized hair cells. The exocarp (peel) contains volatile oil glands (essential oils) in pits. Fig. 2a shown a cross-section of citrus fruit (*C. limon*). The close-up view of peel (exocarp) of a citrus rind is as shown in Fig. 2b, it has numerous pits producing and storing volatile oil glands. The known citrus fragrance given off is the essential oils (terpenes and phenolic compounds) in the pits when citrus peels are processed, bruised or ground. The aromatic perfume comes from the rinds of citrus. Besides citrus peel, essential oils in the pits of skins which are extracted by maceration and modern hydraulic presses and is also one of the important by-products of citrus [11].

Phytochemical of citrus peel: Citrus peels naturally abundant with phytochemicals such as phenolic acids and flavonoids. The main citrus flavonoid was flavanones such as nobiletin, tangeretin, hesperidin, rutin and naringin [12]. Among a few applications of these flavonoids are as antioxidant which will lead to anticancer, anti-inflammation, *etc*. The antioxidant properties are usually elucidated on its ability to suppress the development of rancidity in fats and oils generally. Issues and awareness regarding synthetic antioxidants (BHT and BHA) being toxic and having carcinogenic effects are rising [13]. Hence, there is a strong demand for natural sources as an effective alternative [14,15] and citrus fruits are a good source of many natural compounds. Thus, besides reviewing by-products of citrus fruits' pharmacological properties, identification and isolation of bioactive compounds from citrus peel is adding value to both research and industries [14]. Table-1 indicates the flavonoids present in citrus peel [16].

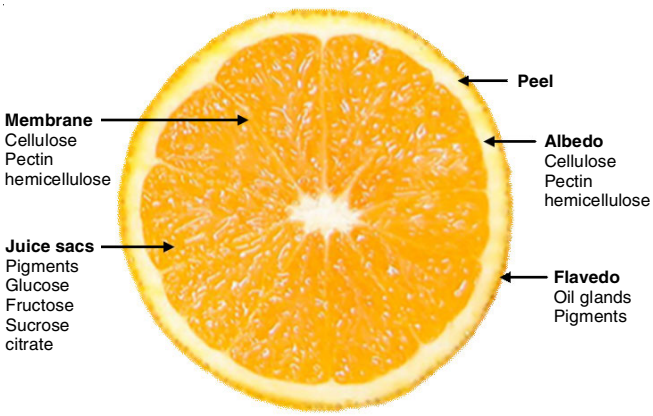

Fig. 1. Cross-section of *C. reticulata* [Ref. 10]

TABLE-1
FLAVANOIDS OF CITRUS PEEL [Ref. 16]

Flavanone	
Eriocitrin (ERC)	R=rutinose, R_1=OH, R_2=H
Neoeriocitrin (NER)	R=neohesperidose, R_1=OH, R_2=H
Narirutin	R=rutinose, R_1=R_2=H
Naringin (NRG)	R=neohesperidose, R_1=R_2=H
Hesperidin (HSP)	R=rutinose, R_1=OH, R_2=Me
Neohespiridin (NHP)	R=neohesperidose, R_1=OH, R_2=Me
Neoponcirin (NPO)	R=rutinose, R_1=H, R_2=Me
Poncirin (PON)	R=neohesperidose, R_1=H, R_2=Me
Flavone	
Rutin (RTN)	R=H, R_1=OH, R_2=H, R_3=O-rutinose
Isorhoifolin (IRF)	R=rutinose, R_1=R_2=R_3=H
Rhoifolin (RFN)	R=neohesperidose, R_1=R_2=R_3=H
Diosmin (DSM)	R=rutinose, R_1=OH, R_2=Me, R_3=H
Neodiosmin (NDM)	R=neohesperidoside, R_1=OH, R_2=Me, R_3=H
Polymethoxylated flavone	
Sinensetin (SNT)	R=H, R_1=OMe, R_2=H
Nobiletin (NOB)	R=R_1=OMe, R_2=H
Tangeretin (TNG)	R=OMe, R_1=R_2=H
Heptamethoxyflavone(HPM)	R=R_1=R_2=OMe

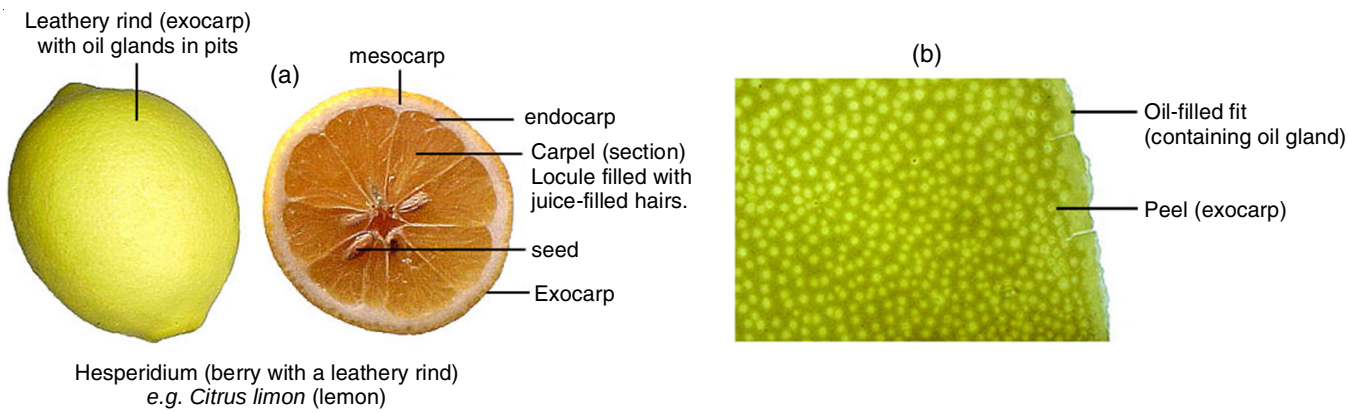

Fig. 2. (a) Cross-section of *C. limon* (b) Magnified view of *C. limon* peel [Ref. 10]

Phenolic acids: Phytochemicals are the major bioactive compounds known to have potential therapeutic benefits especially the one from plant origin. Phenolic acids are very common in plants, not only in edible parts but also found in non-edible parts of the plant, peel for example. For a balance nutrition intake, fruits and vegetables play a major role and they are the major sources of polyphenol [17]. Food and agricultural products processing industries produce substantial quantities of pheno-lics rich by-products, which have gained much attention due to their antioxidant behaviour and beneficial health properties in chronic and degenerative diseases. These products are gaining popularity due to public awareness and their pharmacological potential in anticancer, antidiarrheal, antihypocholesterolemic, antiobesity, antidiabetic, antioxidant, anti-inflammatory and antiosteoporosis [18].

Flavonoids: Flavonoids are diphenolpropanoids which naturally abundant in plant foods and are very important for human diet. Recently, interests in flavonoids have been increasing. Although flavonoids are generally considered to be non-nutritive agents, attention to them arisen due to their potential role as anticancer, antidiarrheal, antihypocholesterolemic, anti-obesity, antidiabetic, antioxidant, anti-inflammatory and anti-osteoporosis.

Flavonoids are strong antioxidant [19,20] and scavengers of free radicals [21] involved in cell damage and mutation [17,22,23]. Table-2 shows the comparative flavonoids in citrus

TABLE-2
COMPARATIVE FLAVONOIDS IN CITRUS PEEL AND THEIR RESPECTIVE PHARMACOLOGICAL PROPERTIES

Citrus peel	Flavonoids	Methods of extraction/isolation	Mechanisms of action	Pharmacological properties	Ref.
C. unshiu	Nobiletin	Cold-pressed oil were processed by an FMC in-line juice extractor and isolated by silica gel column chromatography	Inhibition of inflammation, angiogenesis and induction of apoptosis	Anticancer against skin, colon, prostate, lung and liver cancer	[32]
C. sinensis *C. hassaku* *C. limon* *C. natsudaidai* *C. miyauchi* *C. satsuma*	Nobiletin Sinesetin Tangeretin Naringin Hesperidin Hexamethoxy flavone Tetramethoxy flavone Heptamethoxy flavone	Gold lotion (GL) with 6 different citrus was formulated and used in cancer treatment via western blot analysis	Inhibition of inflammation and angiogenesis in skin model	Anticancer in inflammation-associated tumorigenesis treatment	[33]
Commercial sweet orange peel extract	Sinesetin Hexamethoxy flavone Nobiletin Tetramethoxy flavone Heptamethoxy flavone Tangeretin	Cold-pressed citrus peel oil and was later purified with a flash chromatography system on a silica gel column	Cytoprotectivity level reduced, MTT assay	Anti-inflammatory	[44]
C. aurantium L.	Hesperidin	Hesperidin was isolated from citrus' rind. (Isolation method was not stated)	Animal model (rat paw edema), detection on paw swelling	Anti-inflammatory	[45]
C. paradis *C. kotokan* Hayata *C. limon* (i.) Bur *C. sinensis* (I.) Osbeck *C. reticulata* x *C. sinensis* *C. reticulate* Blanco *C. tankan* Hayata	Hesperidin Naringin Neohesperidin Narirutin Nobiletin Sinensetin tangerentin	Methanolic extraction	Inhibited PGE_2 and NO production primarily through transcriptional regulation of COX-2 and iNOS genes	Anti-inflammatory	[46]
C. medica Linn	Non-stated	Water extraction	Inhibit growth of microbes	Antidiarrheal	[49]
C. limon	Non-specific flavonoids were stated	Hexane extraction by powderised citrus peel	Wet fecel inhibition method (blockage of β adrenergic receptors and inhibit intestinal fluid accumulation)	Antidiarrheal	[50]
C. sinensis	Non-specific flavonoids were stated	Cold water extraction, centrifuged and the supernatant was collected	Level of glucose serum and antiperoxidative activity	Antidiabetic	[60,62]
Navel orange (Scientific name was not stated)	Naringin Naringenin	Hydroethanolic extraction	Levels of serum insulin and C-peptide, expression of adiponectin, GLUT4 and insulin receptor in adipose tissue, liver content of glycogen and liver activities of glucose-6-phosphatase and glycogen phosphoroylase	Antidiabetic	[65]

C. medica cv Diamante	Non-specific flavonoids were stated	Ethanolic extraction. No isolation was conducted	Glucose homeostasis and metabolism. Inhibit carbohydrate-hydrolysing enzyme, stimulation of insulin and metabolic effect in animal model.	Anti-diabetic	[66]
C. limetta	Non-specific flavonoids were stated	Water-extraction	Inhibit carbohydrate hydrolysing enzyme	Anti-diabetic	[67]
C. reticulata Blanco cv. Egyptian *C. sinensis* (L.) Osbeck cv. Olinda Valencia *C. paradisi* Macfad cv. Duncan *C. aurantiifolia* Swingle cv. Mexican	Nobiletin	Hexane extraction prior to isolation via silica gel column chromatography	Lowering cholesterol level in animal model	Anti-hypocholesterolemic	[68]
Tangerine (Scientific name was not stated)	Tangeretin Nobiletin Sinensetin	Hexane extraction	Lowering cholesterol level in animal model	Anti-hypocholesterolemic	[70]
C. depressa Hayata	Nobiletin	Methanolic extraction prior to isolation via silica gel chromatography	Decrease body weight gain, and white adipose tissue, triglyceride level, plasma cholesterol and glucose levels. Prevent reduction in bone material density	Anti-obesity Anti-osteoporosis	[72]
C. depressa Hayata	Nobiletin	Methanolic extraction prior to isolation via silica gel chromatography	Improves insulin resistance, glucose metabolism, plasma glucose and adiponectin level.	Anti-diabetic Anti-obesity	[74]
C. depressa Hayata	Nobiletin Tangeretin	Methanolic extraction prior to isolation via silica gel chromatography	Regulate lipid metabolism, plasma cholesterol and triglycerides levels, low level of weight gain, and visceral fat pad,	Anti-obesity	[78]
Non-stated	Nobiletin	Commercial nobiletin	Prevent bone resorption by inhibiting NFκB-dependent prostaglandin E synthesis in osteoblasts	Anti-osteoporosis	[80]

peel and their respective pharmacological properties elucidated by various group of researchers.

Pharmacology of citrus peels: Citrus fruits are commonly known for their uses in the field of culinary and even medical. Hesperidin, narigin, nobilentin, tangeretin, neoponcirin, narirutin and diosmin among others are common flavonoids naturally abundant in citrus [24-26]. In this review, common flavonoids from citrus peel are being bibliographically studied on their pharmacological potentials. There are three subclasses of citrus flavonoids existing abundantly in citrus peels, they are polyhydroxyflavonoids, polymethoxyflavonoids and mixed substituted flavonoids with both hydroxyl and methoxyl groups, particularly 5-demethylated polymethoxyflavonoids. Though the natural content of 5-demethylated polymethoxyflavones in citrus peels is low, it has been confirmed that they have higher potency in combating diseases than their non-demethylated counterparts [27,28]. A number of reports have demonstrated the biological properties of these citrus flavonoids including anticarcinogenic, antidiarrheal, antihypocholesterolemic, anti-obesity, antidiabetic, antioxidant and anti-inflammatory properties, which help in enhancing human health [24-29].

Anticancer: It was reported by a handful of researchers [27-31] who had demonstrated citrus peels′ potent anticarcinogenic both *in vitro* and cell or human administration. The investigations through both *in vivo* and *in vitro* were either utilized individually or in combination of citrus flavonoids. The unusual characteristic and feature of citrus peel flavonoids is its high concentration of a diverse assortment of flavonoids. One of the known flavonoids is nobiletin, which is a citrus polymethoxyflavones is known to be effective in combating against skin [32,33], colon [34,35], prostate [36], lung [37] including liver cancer [38,39]. The mechanisms include inhibition of inflammation, angiogenesis and induction of apoptosis [30,31]. Inflammation acts as a driving force in premalignant and malignant transformation which linked to carcinogenesis.

As stated by Murakami *et al*. [32], satsuma mandarin contains approximately 5 times higher amount of nobiletin as compared to other citrus peel varieties. Murakami *et al*. [32] predicted topical or transdermal applications of nobiletin (160 and 320 nmol) can stop the growth of skin tumors *via* animal model induced with phorbol ester in a dose-dependent manner. The mechanisms involve inhibition of inflammation and efficiency

of suppressant (biochemical markers) relating to oxidative stress. Nobiletin has higher chemopreventive ability when comparing to resveratrol in studies on rodent model induced with phorbol ester for skin inflammation, oxidative stress and tumor promotion. They concluded that nobiletin is a novel chemopreventive promoter due to its ability to inhibit tumor growth, inflammation as well as suppress oxidative stress. It also explicits that nobiletin can be found only in citrus fruits. In addition, nobiletin is biochemically stable hence can be produced in bulk quantity for more studies both *in vivo* and *in vitro* for stronger activities [32].

Pan *et al*. [33] studied *in vivo* antitumor of the citrus peel gold lotion product efficiency. The potential mechanism was elucidated involving animal induced with 7,12-dimethylbenz-[*a*]anthracene/12-O-tetradecanoylphorbol- 13-aetate (DMBA/TPA) for two-stage skin carcinogenesis model. In this study, TPA has been used to initiate and promote acute inflammation or as potent tumor inducer. The gold lotion formula is made of six variety of citrus peels with a total flavonoids value of at least 450 ppm or 0.45 mg/mL. It is formerly known that gold lotion was able to treat cancer by topical application in treating melanoma, oral ingestion to treat prostate, lung and liver cancer. A safety evaluation was conducted, and it was reported later in the year of 1986 by Miyauchi Citrus Research Center that gold lotion was non-toxic. The research group [33,36] also discovered that gold lotion formula is effective for the inhibition of transcriptional activation of inducible nitric oxide-synthase (iNOS), its mRNA and protein in rodent skin when applied topically. In addition, pretreatment with gold lotion significantly hindered DMBA/TPA-induced skin tumor size and occurrence including the weight of tumor. Overall, the application of gold lotion significantly inhibited tumor size distribution, especially in tumors with size bigger than 5 mm (large tumor) due to significant decrement in its weight [33,36]. For the investigation of gold lotion antitumors induction activity, western blot analysis was applied by Pan *et al*. [33]. It was reported that the ornithine decarboxylase (OCD) level of protein significantly decreased in gold lotion-treated mice which was induced with DMBA/TPA prior to treatment. Angiogenesis is a process for tumor growth, invasion and metastasis. Angiogenesis usually associates with the generation of new blood vessels from pre-existing vessels for tumor to form, invade and do metastasis. As mentioned in Pan *et al*. [36] report, angiogenesis is triggered by up regulation of vascular endothelial growth factor (VEGF) when being applied to rodent epidermal layer [40]. Meanwhile, angiogenesis′ important mediator and tumor growth is cyclo-oxygensae-2 (COX-2) [41]. In Pan *et al*. [39] study, rodent applied with gold lotion dropped both COX-2 and VEGF levels of protein. Therefore, the decrement demonstration of gold lotion treatment is effective in antitumorigenesis induced by topical application of DMBA/TPA to rodent. The mechanisms involved down-regulation of inflammation, proliferation and angiogenesis. Better yet, after 20 weeks of introducing gold lotion to rodent has negligible toxicity effect even after extended period of treatment [33]. This concludes the potential potent anti-carcinogenic properties of citrus flavonoids.

Janakiram and Rao [34] did a review on colorectal cancer prevention focusing on colorectal cancer as well as its biomarkers and molecular targets. In the tumor microenvironment, starting from the stimulus for cancer cells growth to developmental stages of tumor size. Wang *et al*. [42] reviewed the potential of flavonoids found in citrus peels which covers inhibition of oncogenesis, proliferation, neovascularization and metastasis including apoptosis induction ability. This shows the potential of flavonoids of citrus peel against combating cancer.

Anti-inflammatory: In addition to citrus peels being rich in flavonoids with anticancer potential, citrus peels also possess anti-inflammatory activity [30,43,44]. Tangeretin and hesperidin are commonly known to have the most abundant polymethoxy-flavones in citrus peel and also known widely as potent anti-inflammation agent. Hesperidin inhibits prostaglandin bio-synthesis as well as the release of histamine from basophils, suggesting that this inhibition is due to anti-inflammatory effects of hesperidin [45,46], while tangeretin prevent cytotoxicity in human cell [44].

The mechanism of this process is elucidated by Emim *et al.* [45] and later followed by Huang and Ho [46] while Gosslau *et al.* [44] characterized citrus peels extracts for plymethoxy-flavones potential in anti-inflammatory *via* cytotoxicity MTT assay. Emim *et al.* [45] studied the pharmacological properties of hesperidin in treating inflammation *via* animal model. Mice treated with hesperidin with doses between 50 and 100 mg kg^{-1} was reported to be able in reducing the paw edema induced by carrageenan. Under 5 h, the weight of paw was reduced by 47 and 63 %, respectively which can match with the effect of mice treated with indomethacin at 10 mg kg^{-1}. Therefore, it was concluded that hesperidin has the potential to cure pleurisy induced by carrageenan. In addition, mice pre-treated with hesperidin are reported to be able to reduce abdominal constriction induced with acetic acid by 50 % but give insignificant effect to tail flick response. In addition, no lesions of the gastric mucosae were found in hesperidin-pre-treated rodents. Hence, hesperidin was identified as a potent bio-activator to reduce yeast-induced hyperthermia in animal model. The report shows that hesperidin isolated from citrus peel has potential as a mild anti-inflammatory agent, hence exhibits pharmacological properties [45].

Citrus peel was used traditionally in the form of dried peels. Especially for Chinese traditional medicines and remedies, dried citrus peel was utilized for many benefits, from improving general health to curing diseases. This includes curing respiratory inflammatory syndromes and act as potent anti-inflammatory agent. Huang and Ho [46] did a study on seven citrus fruits to determine the inhibitory effect of peel flavonoids on the production of pro-inflammatory mediators, prostaglandin E2 (PGE2) and nitric oxide (NO), in lipopolysaccharides (LPS)-activated RAW 264.7 cells. Between all seven citrus peels, they found out that Ponkan (*C. reticulate* Blanco) and Tonkan (*C. tankan* Hayata) exhibits significant inhibition on PGE2 and NO secretion. The composition of these two peel extracts was elucidated and the flavanone glycosides and polymethoxy flavones content especially nobiletin, appear with anti-inflammation ability. Therefore, they concluded that the contributing factors towards anti-inflammatory effects was from the polymethoxy flavones of citrus peels [46].

Gosslau *et al.* [44] characterize six different orange peels extracts (OPE) in view of its potential anti-inflammatory effect

of polymethoxyflavones. Characterization and quantification of the selected compounds of range peels extracts is by HPLC. Meanwhile, for elucidating the anti-inflammation effects, nutrigenomics *via* human cell-based TPA-induced monocyte macrophage differentiation model employing U-937 cells and inflammatory surrogate genes was used. They compared heptamethoxyflavone (HeptaMF) and hexaethoxyflavone (HexaMF) on the relationship between chemical profiles and cell viability profiles. The end results obtained based on MTT-assay, dose response and kinetics analysis of range peels extracts with different chemical profiles revealed fewer cytotoxicity effects of polymethoxyflavones (PMFs) as compared to OH-PMFs. The two polymethoxyflavone was made to compare heptamethoxyflavone (HeptaMF) and hexaethoxyflavone (HexaMF) and in which HeptaMF exhibited fewer cytotoxicity effects than HexaMF. Evaluation of anti-inflammatory of heptamethoxyflavone was based on its high amount of cytoprotective where its cytotoxicity value was 14 % while PMFs and OH-PMFs were 52 and 21 %, respectively [44].

Antidiarrheal: Several researchers [47-49] reported that citrus peels gave an outstanding antimicrobial effect against *Escherichia coli*, *Staphylococcus aureus*, *Proteus mirabilis*, *Klebsiella pneumonia*, *Vibrio cholerae*, *Salmonella*, *Shigela* and *Pseudomonas aeruginosa*. *Vibrio cholerae*, *Salmonella*, *Shigela* and *Escherichia coli* are enterotoxins produced and secreted which causes diarrhea [48]. Therefore, with the inhibition of those microorganisms by citrus peel, it proves the effectiveness in combating diarrhea caused by pathogens [49].

Sah *et al*. [49] elucidated the antimicrobial activity of *C. medica* Linn. peel on seven different bacteria including *Psuesomonas aeruginosa* and *Escherichia coli* which are the toxins inducing diarrhea. They reported among parts of citrus plant, citrus peel indicates weak activity in antimicrobial inhibition. In addition, diarrhea is categorized and detected when mucus secretion of the intestine increases. The decrement in reabsorption of water from intestine and alterations in intestinal motility can also be characterized as diarrhea. These occurrences usually followed by increased propulsion [48]. Adeniyi *et al*. [50] reported the citrus peels′ benefits in reducing the occurrences of passage of wet feces. Besides, the inhibition of accumulating intestinal fluid and reduction in intestinal motility by stimulating the β-adrenergic receptors of intestine were also elucidated. The stimulation or inhibition of receptors on the intestine is responsible for the different activities observed, which include secretion and peristalsis. Stimulation of α- and β-adrenergic receptors inhibits the rate and force of intestinal contraction [51,52]. When β-receptors were inhibited, the inhibition of fluid secretion in intestine was significant, hence exerted citrus peels′ antidiarrheal effect [50,53-55]. Therefore, it is determined that adrenergic pathway inhibition aids the blockage of fluid secretion in the gut hence diarrhea occurrence can be stopped [56,57].

Adeniyi *et al*. [50] revealed that *Citrus limon*′s peel extract significantly reduced the frequency of wet fecal pellets in animal model [58]. Hexane extraction of *Citrus limon* peel (HECLP) showed that it reduced the highest percentage inhibition of wet fecal pellets. The mechanism involved was antisecretory and antimotility of adrenergic pathway where the β-receptors were blocked and thus no fluid secretion and intestinal fluid accumulation was insignificant. Hence, *C. limon* peel showed a high potential in combating diarrhea hence it possesses antidiarrheal effects [50,58].

Antidiabetic: Diabetes mellitus is increasing significantly and becoming a common health problem in global scale. The occurrence of this disorder on human population is increasing at an alarming rate. Diabetes mellitus relates to hyperglycemia which is due to lacking secretion of insulin hormone by pancreas relatively due to several factors [59]. The Diabetes Control and Complications Trial (DCCT) Research Group focuses on regulating the level of glucose in blood for catering diabetes mellitus. They studied the beneficial traits of citrus peel on insulin levels, thyroid hormones and glucose level in normoglycemic rodents [60].

Parmar and Kar [61] observed the antidiabetic potential of *C. sinensis* peel extracts in alloxan induced diabetes mellitus male mice for its positive effects on insulin level, thyroid hormones level and glucose level in normoglycemic rodents. Simultaneously, they studied on the alterations in tissue lipid peroxidation (LPO), reduction of glutathione content (GSH), activity of superoxidedismute (SODD) and catalase (CAT) in liver, heart and kidney tissues. Peel extraction was prepared by cold water extraction. They revealed that at dose 25 mg/kg, it maximized the decrement of glucose level and antiperoxidative activities. An appropriate dose of peel extract allowed alloxan treated mice aids in higher serum levels of glucose and β-amylase activity, rate of water consumption and lipid peroxidation (LPO) in hepatic, cardiac and renal tissues with a parallel decrease in serum insulin level, administration of 25 mg/kg was found to normalize all the adverse changes induced by alloxan, revealing the antidiabetic and antiperoxidative potential of *C. sinensis* peel extracts. Total polyphenols of the extracts were determined through subsequent phytochemical analysis. The test showed a high number of total polyphenols in the peel extracts. These results supported the antidiabetic and antiperoxidative effects of the peel extract [62].

Ahmed *et al*. [63] reported the antidiabetic potentials in rodents induced with nicotineamide/streptozotocin for type 2 diabetic effect. According to their reports, naringin and naringenin were extracted from navel orange peel *via* hydroethanolic extraction. These flavonoids can modulate the metabolism of cholesterol as well as gene-expression involving glucose homeostasis, reducing oxidative stress, suppressing absorption of carbohydrate in the gut and inhibit gluconeogenic pathways which will lead to hypoglycemic in patients diagnosed with diabetes [63-65]. The mechanisms of actions were through the monitoring of serum insulin and C-peptide level, expression of adiponectin, glucose transporter type 4 (GLUT4) and insulin receptor in adipose tissue, liver content of glycogen and liver activities of glucose-6-phosphatase and glycogen phosphorylase. As a result, from enhancement in expression of insulin receptor, GLUT4 and adiponectin, it was proven that the important potential in improving tissue insulin sensitivity was for curing diabetes. Therefore, the flavonoids naturally available in citrus peel have antidiabetic potential.

Menichini *et al*. [66] reported both *in vitro* and *in vivo* for antidiabetic potentials of *C. medica* L. cv Diamante peel extract. By examining the inhibition level of α-amylase and

α-glucosidase enzymes, stimulation secretion of insulin and metabolic effects in animal model for the effects of flavonoids, can help in supporting the data claiming that citrus extract has the potential to improve the health status of diabetic patients. Extraction of *C. medica* inhibited both α-amylase and α-glucosidase which were the enzymes for hydrolyzing carbohydrates. The other mechanism involved was effect of stimulation of insulin on the exocytotic secretion caused by peel extract. The administration of citrus extract was able to lower blood sugar concentration and reduce the levels of plasma cholesterol and triglycerides. Therefore, this showed that they obtained results underlining the potential anti-diabetic properties from consuming *C. medica* cv Diamante [66].

Similar to Menichini *et al*. [66], Padilla-Camberos *et al*. [67] also reported the antidiabetic potential of citrus peel extract. It was reported that water extraction of *C. limetta* peel able to inhibit carbohydrate metabolism, primarily inhibition of enzyme α-amylase and β-glucosidase. High value for total phenolic content of *C. limetta* peel (19.1 mgGAE/g) supported the inhibition level of both α-amylase and β-glucosidase enzyme for inhibiting carbohydrate metabolism in diabetes patients. In addition, the antioxidant activity of *C. limetta* peel demonstrated in the report gave a significant value in dose-dependent manner. Studies on these polyphenolic compounds from aqueous extract of citrus peel showed results of having both antihyperglycemic and antioxidant activities. Hence, exhibits a potential in combating type 2 diabetes mellitus [66,67].

Antihypocholesterolemic: Fayek *et al*. [68] studied on hypocholesterolemic effect of citrus peel and the result showed a decrease in cholesterol level equivalent to a reference atorvastatin. Another group of researches [69-72] showed that citrus peel can enhance blood cholesterol profile in dose dependent manner. Bringing down plasma and hepatic cholesterol and triacylglycerol by hindering hepatic enzymes in animal model. The hypocholesterolemic effects is due to the presence of nobiletin, which triggers lipolysis in differentiated adipocytes, weakened dyslipidemia through a decrease in VLDL-triacylglyceride secretion and prevented hepatic triacylglyceride accumulation as well as improved fatty acid oxidation.

Kurowska and Manthey [70] reported the formulations containing citrus flavonoids, mainly tangeretin, hesperidin and naringin, which were assessed for anti-hypocholesterolemic potential in rodents. The rodents′ model was diet-induced hypercholesterolemia. Flavonoids or PMFs metabolites of formulations were also studied. They reported that diets with 1 % PMFs significantly lowered overall serum and very low-density lipoprotein (VLDL) + LDL cholesterol by 19 to 27% and 32% until 40%, respectively. These results showed a high possibility to lower serum triacylglycerols. By feeding a mixture of hesperidin and naringin (1:1, w/w) for 3 %, a comparable reduction can be seen implying lower hypolipidemic potency of hesperidin /naringin when being compared to PMFs. HPLC-MS results distinguished high serum, liver and urine concentrations of tangeretin metabolites including dihydroxytrimethoxyflavone and monohydroxytetramethoxyflavone glucuronides and aglycones. The results of tangeretin derivatives from liver concentrations showed a correlation to hypolipidemic concentrations of intact tangeretin *in vitro*. Therefore, they suggested that PMFs are novel flavonoids with cholesterol and triacylglycerol-lowering potential and that elevated levels of PMF metabolites in the liver would directly responsible for their hypolipidemic effects [70].

Antiobesity: In the previous study, the effects of nobilentin on obesity was investigated and analyzed for its potential underlying mechanisms using obese rodents administered with high-fat diet [73,74]. Nobilentin was reported to lower general body weight gain, white adipose tissue weight and plasma triglyceride and glucose levels. Furthermore, nobilentin increased relative adiponectin levels and glucose tolerance. Nobilentin improves hyperglycemia, hyperlipidemia, insulin opposition and adiposity in obese rodents. Therefore, explaining that nobilentin can direct fat tissue operation and has helpful impacts for the prevention and treatment of obesity. In addition, insulin opposition suppresses lipid collection in adipose tissues. Nobiletin triggers lipolysis in separated adipocytes, and it is most likely to be triggered by cAMP pathway [70,72,75]. Tangeretin manages lipid synthesis by inhibiting the diacylglycerol acyltransferase (DGAT) function and concealing microsomal triglyceride transfer protein in HepG2 cells [70]. Synephrine, an alkaloid extracted from citrus peel has an anti-obesity effect by being a stimulant and its properties are like caffeine and ephedrine. The banning of ephedra has made synephrine a replacement and is widely used as stimulant in fat burners. Synephrine aids weight loss by increasing energy expenditure, metabolism and suppressing the appetite [76,77].

A study done by Lee *et al*. [72] reported that nobiletin stops the increment in body weight, white adipose tissue (WAT) weight and plasma triglyceride in ovariectomized (OVX) C57NL/6J rodents. It has been reported that estrogen can prevent obesity in females. Ovariectomized (OVX) rodents were modeled by steady increased in diet and decreased their activity. When diet intake exceeds energy expenditure, it leads to obesity. When estradiol was administrated to OVX rodents, it was studied that this administration prevented obesity to be further developed. The study was kept control by administrating the same diet for OVX rodents. Thus, it can be concluded that the effect in decrement of body weight gain and WAT weight in this report were not influenced by alterations in diet introduced to the experimental animals. In addition, *in vivo* studies by a handful group of researchers have demonstrated that nobiletin regulates adipogenesis and lipolysis [72-74,78].

For instance, the breakdown of fat cells can be enhanced by nobiletin through activating the cAMP-cAMP response element binding pathway. In addition to suppressing lipid accumulation by downregulating peroxisome proliferator-activated receptor (PPAR)γ and activating AMP-activated protein kinase. However, it was reported that nobiletin can stimulate and increase adipocyte differentiation [75,79]. Moreover, it was stated that nobiletin induced the expression of energy expenditure-related genes, such as PPARα and carnitine palmitoyltransferase I, in HFD-induced obese rodents [72]. According to these reports, the claim stating that when fat breakdown (lipolysis) increased or exceed the total energy burned or energy expenditure, most likely can reduce body weight gain and WAT weight in rodents administrated with nobiletin. However, more studies are needed to support claims on the effects

of nobiletin on the expression of lipid metabolism-related genes. Obesity-related metabolic disorders, for example glucose intolerance, hyperglycemia and hyperlipidemia, are becoming a huge concern in women especially in postmenopausal state. In recent reports, nobiletin reduced plasma TG levels and showed huge potential in reducing plasma T-CHO and glucose levels in OVX rodents. In their previous study, Lee *et al*. [74,78] showed that nobiletin improved hypertriglyceridemia. These results suggested that nobiletin has potential in catering obesity related metabolic disorders.

Antiosteoporosis: It was reported that nobilentin able to regulate bone metabolism by suppressing osteoclast formation and bone resorption induced interleukin (IL)-1 in osteoblasts. Hence, inhibiting bone loss in ovariectomized rodents [72,80]. Osteoporosis means bone porosity, is a skeletal disease which caused by a decrease of strength in bone therefore higher potential for a fracture. Osteoporosis is common in woman after menopause and one of postmenopausal syndrome. Lee *et al*. [72] reported that nobiletin suppressed the reduction in trabecular BMD of OVX rodents and showed tendency to increase total femoral BMD in OVX rodents. They also showed that nobiletin prevents bone loss in OVX rodents. Based on the reported results, nobiletin has high potential as an anti-osteoporosis for postmenopausal women [72].

Pharmacokinetics of compound in citrus peels: Nobiletin, tangeretin and naringin are few of the main flavonoids in citrus. These flavonoids influence several key biological pathways in mammalian cells. Pharmacological potential of nobiletin, tangeretin and naringin have been investigated in clinical trials for human, however, they are limited to studies on glucose homeostasis and cholesterol. Manthey *et al*. [81] studied on tangeritin and nobiletin where they were introduced to rodents through gavage and intraperitoneal injection. Blood serum concentrations of these compounds and their main metabolites were characterized by HPLC-ESI-MS.

The pharmacokinetics study of naringin was performed by Li *et al*. [82] in oral treatment for rodents by using Chaihu-Shu-Gan-San (CSGS) aqueous extract. Non-compartmental model of WinNonlin was utilized to analyze the pharmacokinetics behaviour of naringin. Naringin is characterized as one of the flavonoids with fast metabolism when administrated orally. It was reported that naringin quickly absorbed into serum by reaching the first concentration peak at 15 min and another at 3 hours. However, due to fast absorption, after dosing for 480 min, naringin could not be detected. However, the T1/2? was significantly decreased in rodents administrated CSGS aqueous extract compared with naringin alone. This indicated that naringin in CSGS had higher bioavailability, longer term efficacy and somewhat faster metabolism and excretion than those of naringin. The results also suggested that certain ingredients co-exist in CSGS could influence pharmacokinetic behaviour of naringin. Although this study suggested that the extract of CSGS had better effect than when naringin was alone, it also showed the impressive metabolism of naringin when being compared to nobiletin and tangeretin [82,83].

Conclusion

Concerning the phytochemical and pharmacological properties of citrus byproducts, citrus peel has been reviewed. These citrus byproducts, which are generally discarded as waste, has a promising potential in nutraceutical resources. Citrus and citrus peels are rich in bioactive compounds that are important to human health. The phytochemical from citrus peels have pharmacological activity as anticancer, antidiarrheal, antihypocholesterolemic, antiobesity, antidiabetic, antioxidant and anti-inflammatory properties. However, there is a significant gap remaining to be filled concerning research into citrus peel which holds importance in medicinal values.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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