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Phytochemical compounds and pharmacological activities of lemon (*Citrus limon* L.) – Update Review

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Abstract

The lemon plant (*Citrus limon* L.) is a species from the Rutaceae family that spread from Southeast Asia and spread to all countries in the world. Lemon has been used traditionally since ancient times to treat various diseases and has been tested for various pharmacological activities. The literature review was carried out to study the phytochemical compounds and pharmacological activities of lemon plants. The literature compiled by a minimum of 50 scientific articles using search engines such as Science Direct, Pubmed, and Google Scholar, published for a maximum of the last 10 years, includes a minimum of 20 articles in the last 2 years, has a DOI, and the quality of the journal index is reviewed using Scimago. Lemon is very rich in phytochemical compounds, including flavanones such as hesperidin, eriocytrin, naringin, narirutin, didymin; flavones such as apigenin, luteolin, and diosmin; flavonols such as routine, quercetin, mirisetin, isositrol, limositrol, and limositrin; terpenoids such as limonene, limonoids, and carotenoids. Various kinds of in vivo and in vitro studies provide results of various pharmacological activities such as antioxidants, anticancer, neuroprotective, antimicrobial, antidiabetic, anti-inflammatory, antihyperlipidemic, antiurolithiasis, and antiplasmodial. It is necessary to develop further research on the pharmacological activity of lemon plants in the future.

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INTRODUCTION

Among the various subunits available within the Rutaceae family, the Citrus genus is arguably one of the most important ones. One of the most popular plants of this genus due to its health benefits is the lemon plant (*Citrus limon* L.) (Klimek-Szczykutowicz *et al.*, 2020). Lemon is a type of plant with the characteristic evergreen leaves, which hails from Asia and has yellow edible fruit. The distinctive traits of this type of plant are its thorny branch, white flower, and its oval-shaped fruit with a strong sour taste (Chaturvedi and Suhane, 2016). Lemon originated from Southeast Asia, and then later it spread through the North-Eastern countries such as India, China, and Burmese (Al-Qudah *et al.*, 2018). Due to its versatility, Lemon can be used in a variety of cooking, medicinal, cosmetic, and aromatherapy. Traditionally, lemon juice was used to treat fever, high blood pressure, and menstrual irregularities. Meanwhile, a lemon essential oil is used to relieve coughs. In several studies, it is explained that extracts, essential oils, and lemon juice have pharmacological effects such as antioxidants, anti-inflammatory, antibacte-

rial, neuroprotective, anticancer, and antihyperlipidemic agents (Klimek-Szczykutowicz *et al.*, 2020). These pharmacological effects resulted from the fact that lemon is a plant rich in various active chemical components, especially citric acid, ascorbic acid, flavonoid, and other essential oils (Makni *et al.*, 2018).

MATERIALS AND METHODS

The review of the chemical compounds and pharmacological activities of the lemon plant (*Citrus limon* L.) was conducted by collecting and compiling the relevant literature according to the following keywords in English as *phytochemical compounds lemon, pharmacological activity lemon, traditional use lemon, antioxidant lemon, anti-inflammatory lemon, antibacterial lemon, anticancer lemon, neuroprotective lemon, antidiabetic lemon, anti hyperlipidemia lemon, antimalaria lemon,* dan *anti-urolithiasis lemon*. Minimum 50 articles were collected by using the available search engines, which were Science Direct, PubMed and Google Scholar, published in the last 10 years, consisted of 20 articles from the last 2 years, have DOI and the quality of articles were also reviewed by using Scimago.

TRADITIONAL USES

It is a long-held belief that the lemon plant carries multiple benefits to treat various ailments. The trend for self-medication has shifted a lot these past few years. Generally, people now learn more about herbal medicines and their derivatives rather than synthetically produced medicine. In several ethnic groups, dried lemon fruits are grinded down to powder and used to maintain dentally (Rauf *et al.*, 2014). Lemon plants have long been used traditionally to treat kidney stones, topical dermal problems, UTIs, obesity, digestive problems, respiratory diseases, and even psychosis. Traditional uses of lemon were presented in Table 1.

PHYTOCHEMICAL COMPOUNDS

Multiple studies have been done to analyze the chemical content of the lemon fruit, especially related to its secondary metabolites. The phenolic group compounds, particularly flavonoids, are of abundance in the lemon fruits. The lemon fruits was discovered to contain such as citric acid, ascorbic acid, terpenoids, carotenoids, minerals, and essential oils (González-Molina *et al.*, 2010). The flavanones and flavone glycosides from flavonoids occurred in a significant amount in the flesh of lemon fruits (Ballistreri *et al.*, 2019). In the flavanones group, the highest concentration of hesperidin can be found in the rind of lemons, followed by eriocitrin, narirutin, naringin, and didimin (Barreca *et al.*, 2017). In the flavones group, the C-glycosides such as 6,8-di-C-glucopyranosyl-apigenin and 6,8-di-C-glucopyranosyl-luteolin can be found on the ether petroleum extract, and diosmetin-7-rutinoside can be found on the ethyl acetate extract of lemon rinds (Singh *et al.*, 2020).

Research by Singh *et al.* (2020) presented the flavonols group such as rutin, quercetin, myricetin, isocitrol, limocitrol, and limocitrin can also be found on the ethyl acetate extract of lemon rinds in a small amount. Other compounds from the flavonols group can be identified in the flesh of lemon fruits such as quercetin glycoside (Ledesma-Escobar *et al.*, 2019). Rafiq *et al.* (2018) demonstrated that the terpenoid group such as limonene may be determined on lemon rinds and limonoid in the lemon juice (Rauf *et al.*, 2014) and seed (Shi *et al.*, 2020). Tetraterpenoids such as carotenoids were exposed in a considerable amount on lemon rinds (Guimarães *et al.*, 2010). Mineral content such as Ca, K, Na, Mg, Zn, and Fe may also be presented on lemon rinds (Ghanem *et al.*, 2012). A study by González-Molina *et al.* (2010) showed that twigs, leaves, fruits, flowers, seeds, and roots of lemon plants had essential oils such as d-limonene, citral and linalool. The structure of chemical compounds isolated from the lemon was expressed in Figure 1.

PHARMACOLOGICAL ACTIVITIES

Antioxidant activity

Free radicals are reactive molecules which possess one or more unpaired electron on its outer layer, free radicals' characteristics are unstable, very reactive, and tend to attack other molecules such as lipids, carbohydrates, and proteins. The production and accumulation process of free radicals inside the human body must meet a certain equilibrium. Otherwise, there may be a phenomenon called oxidative stress, which is described as the imbalance of the number of free radicals inside the human body (Pizzino *et al.*, 2017). Oxidative stress may cause the degradation of DNA, cells, organelles, and other biomolecules, which will lead to numerous health problems such as cardiac diseases, ageing, hypertension, inflammation, and even cancer (Olszowy, 2019). Antioxidants are compounds with a certain molecular structure that can donate their electrons to the free radical molecules, which in turn will break the chain of the oxidative process (Gülçin, 2012).

Antioxidant activity from the liquid ethanol

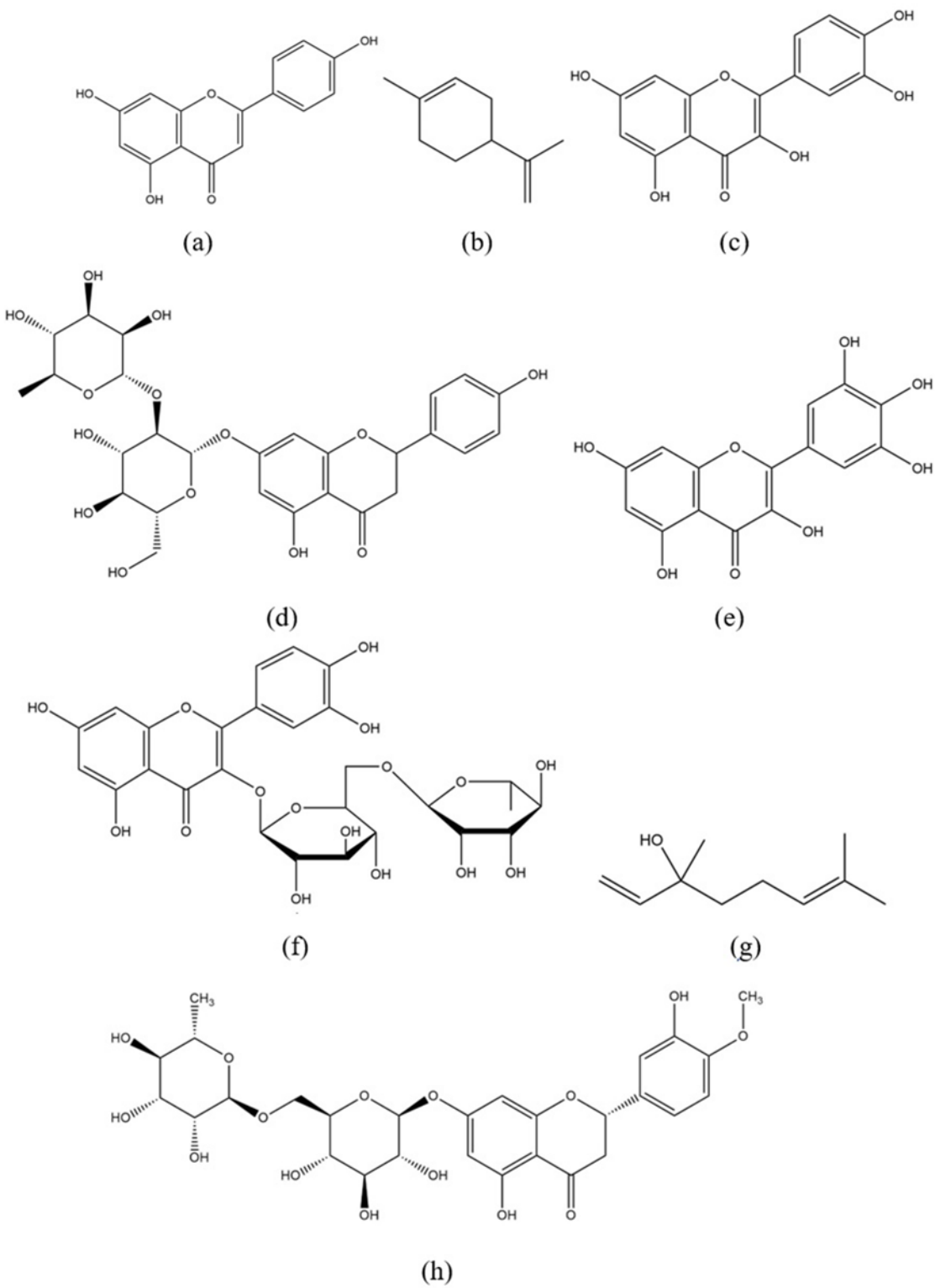

Figure 1: Structure of chemical compounds isolated from lemon. (a) apigenin; (b) d-limonene; (c) quercetin; (d) naringin; (e) myricetin; (f) rutin; (g) linalool; (h) hesperidine

Table 1: Traditional uses of lemon

Plant Part	Traditional Uses	Reference
Lemon juice with olive oil	To treat gall bladder and kidney stones.	(Chaturvedi and Suhane, 2016)
Lemon juice	To brighten the skin's appearance due to the abundance of vitamin C.	(Chaturvedi and Suhane, 2016)
Lemon juice and lemon oil	May be of use orally to rejuvenate skin and prevent infection. May be of use topically to shed the outer dead skin layer, treat dandruff, and treat rashes.	(Mohanapriya *et al.*, 2013)
Lemon juice	To treat urinary tract infection (UTI).	(Chaturvedi and Suhane, 2016)
Lemon juice	To eliminate the deposit of stones in the kidney and urinary bladder. To treat urinary tract infection (UTI).	(Mohanapriya *et al.*, 2013)
Lemon juice with honey	To aid with weight loss.	(Chaturvedi and Suhane, 2016)
Lemon juice with a glass of warm water	To treat obesity with the mechanism of breaking apart the adipose tissue and visceral fat, and also regulate hunger due to pectin.	(Mahmood *et al.*, 2019)
Lemon peel	To treat obesity in children and adolescents.	(Mahmood *et al.*, 2019)
Pickled Lemon	To aid digestion process by stimulating the secretion of digestive juices, bile acid, and stimulating the peristaltic wall movement in the digestive tract.	(Mohanapriya *et al.*, 2013)
Lemon oil	To be used as an anti-congestive agent	(Mohanapriya *et al.*, 2013)
Lemon peel	To relieve congested nasal cavity and aid with nausea by inhaling the lemon peel.	(Mohanapriya *et al.*, 2013)
Lemon oil	To treat dementia symptoms and as an alternative for antipsychotic.	(González-Molina *et al.*, 2010)

extract of lemon rinds exposed 80.93 mg Trolox/100 g lemon rinds with the 2,2-diphenyl-1-picrylhydrazyl (DPPH) analysis method and 451.56 mg Trolox/100 g lemon rinds with the 2,2'-azino-bis 3-ethylbenzothiazoline-6-sulfonic acid (ABTS) analysis method (Casquete *et al.*, 2015). The phenolic-free methanol extract of lemon fruits with heating to 60°C (FP60) had a higher amount of antioxidant, which was 43.7%, compared to the phenolic-fee methanol extract with heating to 30°C (FP30) 33.8% (Alu'datt *et al.*, 2017). In the polar fraction of lemon rinds with methanol as solvent, EC_{50} was discovered 3.77 mg/ml by using DPPH. This is due to the fact that the activity of antioxidants is parallel to the number of phenols, flavonoids, ascorbic acid, and carotenoids (Guimarães *et al.*, 2010). A study has already been done only by analyzing the essential oil content of lemon fruits from Argentina, the United States, and commercials, and the result showed a substantial activity value of antioxidant by using the DPPH method, in the range of 20-28 mg Trolox Equivalent (TE)/ml citrus essential oil (CEO), and 6.7-7.6 mg TE/ml CEO by using CUPRAC method (Raspo *et al.*, 2020).

This antioxidant activity is caused by the presence of secondary metabolites, which plays a role in the process of capturing free radicals. The naringin, hesperidin, naringenin, quercetin, rutin, coumarin, and phenolic acid from the phenolic group had their own unique antioxidant activity. The compound limonoid, carotenoid from the terpenoid group, and essential oils also gave rise to a diverse antioxidant activity (Zou *et al.*, 2016).

Anticancer

Cancer is one of the most deadly diseases which has caused numerous death around the world. There are plenty of reports regarding the efforts done to develop an efficient medication to treat cancer (Yi *et al.*, 2017). Most of the established medicine was

used to treat cancer now are synthetically developed. Nowadays, natural products are in high demand and interest in the field of drug discovery (Mondal *et al.*, 2012). The phytochemicals are of high interest to treat cancer due to the fact that they have low toxicity, relatively high bioavailability, and safety parameters (Agyare *et al.*, 2018). An epidemiology study stated that consuming a certain amount of fruits and vegetables in a long period of time may reduce the risk of chronic diseases such as cancer (Key, 2011).

Lemon fruits contain an abundance of secondary metabolites from the phenolic group, such as flavonoids. The compounds from the flavonoid group, such as flavanones obtained from Citrus, were known to have anticancer activity according to numerous *in vitro* and *in vivo* studies. A study proved that flavonoids not only act as an acceptor of free radicals but also as a modulator for several molecules pertaining to the human cell's life cycle. The naringin and naringenin compounds from Citrus rinds were shown to possess antiproliferative activity to cancer cells such as breast, stomach, liver, pancreas, cervix, and colon cancer cells. Hesperidin also exposed an inhibitory effect on the cell's development phase on Panc-28 cells or human pancreatic cancer cells. Moreover, hesperidin gave an inhibitory effect on the proliferation of Ramos Burkitt from the lymphoma cells (Cirmi *et al.*, 2016). A study with the subjects of rats with N-nitrosodiethylamine-induced hepatocarcinogenesis presented that naringenin exhibited inhibitory action of cell proliferation, even inducing cell apoptosis (Arul and Subramanian, 2013). Another isolated study nanovesicles from lemon juice with size and cargo properties comparable to exosome-like nanoparticles. The *in vivo* and *in vitro* studies figured that they inhibited the growth of tumor cells without affecting the normal cells. The mechanism of action towards the colon cancer cells was by reducing the regulation of acetyl-CoA carboxylase involved in the first step of de novo fatty acid synthesis, thus reinforcing the theory of involvement of lipid-enzymes towards tumor growth (Raimondo *et al.*, 2018).

The limonoid compounds found in lemon rinds exposed give an effect to cell proliferation from colorectal, stomach, pancreas, breast, and prostate. The limonin from the limonoid group had undergone extensive experiment, which resulted in its inhibitory activity in the intestinal polyp cells from Apc-mutant rats (Shimizu *et al.*, 2015). Limonin also exhibited an inhibitory activity to the proliferation of the hepatocellular carcinoma cell (Rahman *et al.*, 2015). Limonoid represented the effect of increasing the detoxification process pertaining with the 2^{nd} phase enzymes such as glutathione S-transferase (GST) and nicotinamide adenine dinucleotide phosphate (NAD(P)H), which may remove toxic molecules such as carcinogens, chemotherapeutic agents, environmental pollutants, and products from the oxidative stress process (Dasari *et al.*, 2018).

Neuroprotective

Functional damage of neurons and neurodegenerative diseases may occur due to multiple factors contributing to the nerve cells' degenerations. One of them is oxidative stress which will accelerate the symptoms. The high metabolic activity coupled with the low antioxidant defence mechanism in the brain's neural cells will render them more susceptible to oxidative stress, especially in mature neuron cells. Flavonoids in lemon fruits were neuroprotective agents with the mechanism of capturing free radicals, increasing cellular endogen antioxidants, and activating the pro-survival route, thus allowing them to combat the oxidative stress effects (Hwang *et al.*, 2012).

Hesperetin (0.1 μM) was shown to have a protective effect towards cortical neurons from oxidative damages through the activation of pro-survival Akt and ERK1/2 route and inhibit pro-apoptosis protein activation such as apoptosis signal-regulating kinase-1 (ASK1), caspase-9, Bad, and caspase-3. The neuroprotective mechanism of limonin was by combating the glutamate's toxicity, the study done by using rat's cortical cells. Limonin (0.1 μM) effectively weakens the glutamate-induced neurotoxicity with cell viability of 65.8%, while the viability of the glutamate-induced damaged cells 0%. Moreover, limonin was able to activate the antioxidant enzymes that act as neuroprotectors and its usage recommended for degenerative neural diseases related to glutamate (Yoon *et al.*, 2010).

Hesperidin was a potent antioxidant that acts as a stabilizer of bio-membrane, which will cause a protective effect for patients with Parkinson's disease through the mechanism of antioxidant and increment of dopamine (Antunes *et al.*, 2014). Other than that, hesperidin exhibited a modulatory activity towards the Kapp receptor (K-opioid) and serotonergic 5-HT1A, which may reduce the symptoms of depression (Souza *et al.*, 2013). Hajialyani *et al.* (2019) presented that hesperidin may be used to treat dementia and Alzheimer's disease, Huntington's disease, multiple sclerosis, and diabetes-mellitus-associated neurotoxicity.

Antimicrobial

A bacterial infection may develop into more severe and diverse clinical problems. The antibacterial resistance phenomenon is to blame for the decrease of potent antimicrobial agents. Plant-derived essential oils were a prospective agent and high advantage to develop into antimicrobial agents. Numerous studies showed the antimicrobial activity of plant-derived compounds. The essential oils content, particularly limonene from lemon fruits, was known to possess antimicrobial activity. In a study which was done by using essential oil (1 μg/ml) to determine the antimicrobial activity by the disc-diffusion method on *Micrococcus flavus, Bacillus subtilis, Staphylococcus epidermis, Staphylococcus aureus, Salmonella enteritidis, Salmonella typhimurium, Escherichia coli, Enterobacter cloacae, dan Listeria monocytogenes.* The result showed that the inhibition zone ranged from 9 to19 mm, with the highest value for the *M. flavus* (Soković *et al.*, 2010).

The 5-geranyloxypsolaren, 5-geranyloxy-7-methoxycoumarin, 8-geranyloxypsolaren, and phlorin compounds had been isolated successfully from the methanol extract of lemon rinds (Miyake and Hiramitsu, 2011). All the compounds are then tested to determine the antimicrobial activity towards *Prevotella intermedia, Porphyromonas gingivalis*, and *Streptococcus mutans* which then will be translated to minimum inhibitory concentration (MIC) given in Table 2.

Antidiabetic

Diabetes mellitus is a chronic metabolic disease with the synonym hyperglycemia, type 1 of DM is caused by insufficient insulin production (Chukwuma *et al.*, 2018), while type 2 of DM is caused by the unresponsive cells towards insulin, thus hindering its work (Erukainure *et al.*, 2019). Diabetes mellitus was the main cause of mortality due to certain unhealthy lifestyles, which lead to obesity (Farzaei *et al.*, 2017).

There are 19 main Citrus flavonoid compounds that have been studied and exhibited antidiabetic effects. The phytochemical compounds contained within the lemon fruits which exhibited antidiabetic activity were hesperidin, didimin, quercetin, naringin, and rutin (Gandhi *et al.*, 2020).

The hesperidin compound has been studied by using Wistar rat with diabetic symptoms induced by streptozotocin (STZ), and the result showed it exhibited the lowering of the glycolic amount in blood effect and regulating the glycolic-liver regulating enzyme activity (Akiyama *et al.*, 2009). *In vitro* study by using insulin-resistant HepG2 cells resulted in the fact that didimin was able to inhibit α-glucosidase and activate the insulin signalling route, which in turn will produce insulin with better sensitivity (Ali *et al.*, 2019). The molecular mechanism of quercetin in an *in vitro* study of the skeletal muscle cell (L6 myotubes) indicated the uptake of glucose through the AMPK regulation route and the expression of type 4 (GLUT4)/AKT glucose transporter to induce the uptake of glucose in the skeletal muscle (**?**). The compound naringin exposed antidiabetic activity in a study with fructose-induced endothelial dysfunction in rats. Naringin showed to increase the serum level of nitrate/nitrite (NOx), ENOS, and the expression of p-eNOS, also provide a relaxation effect depending on the rats' aorta induced by fructose (Malakul *et al.*, 2018). The rutin compound expressed to be able to lower the level of blood sugar in Wistar rats, which have been induced with streptozotocin (STZ) by injecting the compound intraperitoneally (Fernandes *et al.*, 2010). In the lemon fruit flesh extract without the exocarp, containing free phenolic compounds with the temperature of 30^o C, a study had observed an antidiabetic activity by inhibiting 100% the action of α-glucosidase (Chukwuma *et al.*, 2019).

Anti-inflammatory

Inflammation is a result of bodily response towards external stimuli, such as bleeding, tissue damages, and pathogen-induced infection. The most common symptoms of inflammation are redness, edema, pain, fever, and functional loss. Normally, inflammation response is a self-induced process to heal the tissue's structure and function, but when an abnormal inflammation mechanism occurs, it may induce permanent damage to the tissue, which may lead to more diverse diseases. The discovery of an anti-inflammatory medicine derived from plants nowadays is of high interest. It was known that the flavonoid of Citrus revealed an anti-inflammatory effect according to the *in vivo* and *in vitro* studies (Yi *et al.*, 2017) .

In a recent study, mice were used by injecting formalin on their legs to induce an inflammation response, and the observed response to the inflammation was the licking behaviour of their legs. Afterwards, the essential oil extracted from the lemon plant was injected through subcutaneous to observe any lessening of the licking response. The result showed that with the highest concentration (100 mg/kg), the licking response was observed to lessen, this phenomenon due to the high limonene content of the essential oil, up to 53.9% (Amorim *et al.*, 2016).

The lemon fruits contained hesperidin, an *in vivo* study using mice with ovalbumin-induced asthma was administered hesperidin (1-5 mg/kg p.o. three times a week) showed that the administration of

Table 2: Minimum inhibitory concentration of isolated compounds in lemon

Isolated compounds	MIC (mM)			Reference
	P. intermedia	*P. gingivalis*	*S. mutans*	
5-geranyloxypsolaren	0.30	0.15	0.15	(Miyake and Hiramitsu, 2011)
5-geranyloxy-7-methoxycoumarin	0.30	0.45	0.30	
8-geranyloxypsolaren	0.30	0.30	0.15	
Phlorin	0.90	3.50	3.50	

hesperidin could reduce the eosinophilic hyperresponsive effect, lung's bronchoalveolar fluid inflammation, and reduce the serum level of IgE and Th2 ovalbumin specific cytokines (IL-3, IL-4, dan IL-5), thus exhibit the regulatory effect towards lung response. A similar result was achieved by hesperidin administration orally (10 and 30 mg/kg for one day) or intranasally (for 10 days) to mice before ovalbumin administered. The result showed a similar inhibitory effect of inflammatory cell infiltration and mucus hypersecretion (Tejada *et al.*, 2019).

Antihyperlipidemic

Hyperlipidemia is a condition where the lipid metabolism is abnormal, sometimes accompanied by troubles with fat transport so that metabolic and endocrine disruption occurs. The main symptom of hyperlipidemia is the high serum/plasma level of triglycerides and cholesterol (Gao *et al.*, 2020).

Studies using mice with the induction of low-fat diet, high-fat diet, and high-fat diet with the administration of D-limonene (0.5% w/w or equal to the dosage 0.6 gr/kg bw), showed decreasing in the level of low-density lipoprotein (LDL) and increased level of high-density lipoprotein (HDL) on mice with the high-fat diet group. This effect was mediated with the PPARα activation and LXRβ signal inhibition. Hence it was inferred that D-limonene could be applied as anti-hyperlipidemic (Jing *et al.*, 2013).

In a study using rats with the highest possible cholesterol level, the powdered methanol extract of citrus rind flavonoid was given orally (600 mg/kg). The result showed that on the 56^{th} day, the plasma triglyceride level was effectively decreased, validated by comparing it to the control group. The flavonoid from Citrus was known to prevent the conjugation of oleic acid from triglycerides. Hence the overall effect was decreasing in plasma cholesterol (Ashraf *et al.*, 2017). The compounds from the flavanone group, such as hesperidin and naringin in lemon fruits, possessed a mevalonate functional group. They resembled statin structurally and seeing as statin is an established drug used to treat hyperlipidemia by inhibiting cholesterol biosynthesis. These compounds could exhibit their anticholesterolemic activity by the same mechanism (Barreca *et al.*, 2017).

Other pharmacological activities

A previous study using Wistar rats in a urolithic condition induced by ethylene glycol (0.75%) compared to the group which administered with lemon peel extract (100 mg/kg bw) orally. The lemon peel extract significantly inhibited the crystal formation, reducing proteinuria and lipid peroxidation. In a curative study, the crystal previously formed could be reduced by giving lemon peel extract, which was rich in flavonoid content, thus inferred that lemon peel extract may be a potential candidate for anti-urolithiasis (Sridharan *et al.*, 2016).

Ruiz *et al.* (2011) carried out *in vitro* study to demonstrate the antimalaria effect towards Amazon inhabitants from the Nanay River (Peru). The liquid-ethanol extract (70:30) of lemon fruits was used against *Plasmodium falciparum* chloroquine-resistant strain (FCR-3). The result presented the antiplasmodial effect with IC_{50} value 4.9 μg/ml. It should be noted that IC_{50} <10 μg/ml was the threshold of the antiplasmodial candidate.

CONCLUSION

The lemon plants were proven to be abundant in their phytochemical compounds, particularly the compound groups flavonoids, terpenoid, minerals, and essential oils, which can be found throughout the whole part of the lemon plant, but mostly concentrated in the lemon flesh and peel. Traditionally, lemon plants have been utilized in a diverse manner, such as treating skin problems, kidney stones, UTI, obesity, digestion, respiratory disease, antipsychotic. The lemon plants have also been studied and shown to exhibit numerous pharmacological activities such as antioxidant, anticancer, neuroprotective agent, antimicrobial, antidiabetes, anti-inflammatory, anticholesterolemic, anti-urolithiasis, and antiplasmodial activities. Thus

can be concluded that the lemon plants were a strong candidate for natural medicinal source, and further studies are needed.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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