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A review on Active Constituents and Pharmacological Effects of *Eriobotrya Japonica* Lindl. (Loquat)

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Abstract

Eriobotrya japonica Lindl., named as loquat, is a subtropical fruit tree of the family Rosaceae which is well known medical plant originated in Japan and China. Loquat portions, like leaves, peels and fruits have been shown to possess various health usefulnesses. In Chinese classical medicine, it is vastly utilized in many illnesses, like gastroenteric disorders, diabetes mellitus, pulmonary inflammatory diseases and chronic bronchitis. Loquat plant contains many active constituents, such as carotenoids, vitamins, polyphenolic compounds, others that have many biological effects like anti-tumor, anti-diabetic, anti-inflammatory, anti-mutagenic, antioxidant, antiviral, antitussive, hepatoprotective and hypolipidemic activity.

Keywords: Loquat, Polyphenolic compounds, Pharmacological effects of *Eriobotrya japonica* .

مراجعة للمكونات الفعالة والتأثيرات الدوائية ل *Eriobotrya japonica* Lindl. (لينكي دنيا)

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الخلاصة

Eriobotrya japonica Lindl. ، المسمى بـ لينكي دنيا ، هي شجرة فاكهة شبه استوائية من العائلة الوردية وهي نبات طبي معروف نشأ في اليابان والصين. ثبت أن أجزاء إسكدنيا ، مثل الأوراق والقشور والفاكهة ، تمتلك العديد من الفوائد الصحية. في الطب الصيني الكلاسيكي ، يتم استخدامه على نطاق واسع في العديد من الأمراض ، مثل اضطرابات الجهاز الهضمي ، وداء السكري ، وأمراض الالتهاب الرئوي والتهاب الشعب الهوائية المزمن. يحتوي نبات اسكدنيا على العديد من المكونات النشطة ، مثل الكاروتينات ، والفيتامينات ، ومركبات البوليفينول ، وغيرها من المركبات التي لها العديد من التأثيرات البيولوجية ، مثل مضادات الأورام ، ومضادات السكري ، ومضادات الالتهابات ، ومضادة للطفرات ، ومضادات الأكسدة ، ومضادة للفيروسات ، والسعال ، ووقاية الكبد ، نشاط نقص شحميات الدم.

الكلمات المفتاحية : لينكي دنيا ، مركبات البوليفينول ، التأثيرات الدوائية للينكي دنيا

Introduction

The genus *Eriobotrya*, distributed in sub-tropical and tropical Southern and Eastern Asia, comprises about 26 species [(1)].

Eriobotrya japonica (Thunb.) Lindl. is a green fruit tree of medium sized belong to family Rosaceae. It is usually named as Loquat. It has been implanted for more than two thousands of years, and is native to Japan and China but recently implanted commercially worldwide for over 30 countries, such as Japan, Iraq, Turkey, Spain, Italy, Syria and other. The local English name of the plant (loquat); Arabic (Beshmelah); German (Loquate); French (bibassier); Chinese (luju,biba), *etc*.It attains up to 6 meters or more height, with thick and evergreen oval-oblong leaves. Fruit yellow to orange, pear-shaped, with seeds 3 to 4, long 4 centimeters, and sweet test as in figure (1) [(2)].

Among other fruits, unusually loquat flower in early winter or autumn, and its fruit ripen in early spring or late winter [(3)].

Currently loquat has been utilized in the jam, chutney and jelly preparation, in addition to it is eaten as a fresh fruit [(4)].

Loquat is implanted mostly to fruit production and in the Chinese classical medicine; also its leaf has been utilized [(5)].

Figure 1. Photo of *Eriobotrya japonica* plant

Taxonomical Classification [(6)]**:**

Kingdom = Plantae
Subkingdom = Viridaeplantae
Division = Tracheophyta
Subdivision = Spermatophytina
Class = Magnoliopsida
Order = Rosales
Family = Rosaceae
Genus = *Eriobotrya*
Species = *Eriobotrya japonica* (Thunb.)

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Traditional uses

Eriobotrya japonica is known widely medicinal plant in China and Japan [1] and for 1000 of years, used in folk medicines [2].

The fruits are used as sedative and helpful in alleviated thirst and vomiting and used for wound treatment in China [7]. The flowers considered an expectorant [2], and they are a good source of honey. Traditionally, loquat fruits and leaves are used as expectorant and for treating coughs [8].

Eriobotrya japonica leaves were utilized in the therapy of stomach and lung illness, diabetes mellitus, skin diseases and inflammatory problem [9] and also efficient in dysmenorrhea, phlegm, asthma, headache, chronic bronchitis, and lower back pain [10].

Also leaves of loquat have been considered digestive, antipyretic, and diuretic agents in Japan [4] and used to alleviated nausea time for treating diseases in the, ethno medicine [11].

The leaf decoction was locally put on wounds, cancers and ulcers [1].

Loquat tea is formed from leaves that are roasted for 30 minutes at 350°C, and according to the folk customs, it is commonly used as beverage [12] .

Chemical constituents:

Broad range of important phytochemicals had been detected in loquat, like phenols, alkaloids, cardiac glycosides, flavonoids, mucilage, gums and phytosterol [8].

Many active compounds present in leaves and fruits that are responsible for various biological activity of loquat plant [13]. Fruit enrich with active compounds such as vitamins, flavonoids, phenols, carotenoid and others [14]. Caffeic acid, 4-o-caffeoylquinic acid, neochlorogenic acid, chlorogenic acid, together with 4-hydroxybenzoic acid, protocatechuic acid, *o*-coumaric acid, ellagic acid and ferulic acid have been identified in mature fruits of loquat as major phenolic compounds [15].

The kernel of loquat is rich with tannins, starch, minerals and proteins [16,17]**.**

Phytochemical study reported that the *E. japonica* flowers are good sources of flavonoids and phenolic compounds [18].

Loquat leaf contain phenolic acids like p-coumaric, gallic, caffeic, and ellagic acid and flavonoids like quercetin, epicatechin and catechin [19], in addition to tannins, sesquiterpenes, triterpenes and megastigmane glycosides [18,20].

Oleanolic and ursolic acids (triterpenoid compounds) have been found in flowers and leaves of loquat with different contents based on the type and developmental stage of cultivar [21].

In addition to ursolic and oleanolic acids, *E. japonica* leaves contain maslinic acid, tormentic acid, and corosolic acid [22]. Tormentic acid possess normoglycemic, antiatherogenic, hypoglycemic, anticancer, anti-inflammatory properties; and it decreases the expansion of vascular smooth muscle cell [23].

Four flavonoids, kaempferol 3-O-β-glucoside, quercetin, quercetin 3-O-α-rhamnoside, naringenin and three triterpene acids, ursolic, corosolic and oleanolic acids were the bioactive components of stems of *E. japonica* [18].

Catechin, β-sitosterol, oleanolic acid, cinchonain IIb, β-sitosterol-3-O-β-D-glucopyranoside, lyoniresinol and lyoniresinol 2-a-O-β-D-xylopyranoside are identified and separated from loquat stem barks [1].

By using high performance liquid chromatography, flavones like quercetin derivatives (likely rutin or similar quercetin glycoside) and hydroxycinnamic acid derivatives like chlorogenic acid with other *p*-coumaric acid and caffeic acid derivatives, have been identified in leaves, fruit, flower of loquat but chlorogenic acid has been the main phenolic compound. Flowers possess higher content of quercetin and chlorogenic acid derivatives than new and old leaves. The new leaves possess higher *p*-coumaric and caffeic acid derivatives contents than flowers and old leaves [5].

Pharmacological Activities of Eriobotrya Japonica

Cytotoxic activity

Bushra Alwash (2017) reported that the fruit juice of loquat shown a significant anticancer effect on two cell lines of cancer, rhabdomyo sarcoma (RD) and human cervical cancer (Hela) cell. But the cytotoxic effect of fruit juice was higher on Hela than on RD cell line while on rat embryogenic fibroblast (as a normal cell), the effect of juice was lower than on RD and Hela cancer cell lines [2]**.**

Loquat juice contained active constituents such as terpenoids, phenols, tannins, and flavonoids that have ability to effect on cells.

Studying the anticancer effect of loquat juice on cell lines of cancer demonstrated the highest cell lines sensitivity by stimulation of some glutathione-S-transferase enzymes (GSTs) by many compounds, mainly the polyphenolic compounds in plant extract [24]. The GSTs considered as an antioxidant and by inducing their combination with reduced glutathione causing cellular detoxification and leading to the cells of cancer toward death and apoptosis [24].

So the utilization of *E. japonica* fruit juice to protective the body of human against cancer and free radicals better than use of the extraction methods, in which some effective compounds will be lose during the process of extraction and the poisonous of solvent will be get rid [2].

The ethanol and aqueous leaf extracts of *E. japonica* suppressed 7, 12-dimethylbenz[α]anthracene -stimulated breast cancer and inhibited the cancer development of breast by inhibiting the cancer cells proliferation and initiation in rats. But water extracts displayed a higher anticancer activity [25].

Four triterpenic acids, ursolic , betulinic, δ-oleanolic, and 3-O-(E)-p-coumaroyl tormentic acid (Fig.2), separated from methanol loquat leaf extract exerted cytotoxic effect on human HL60 cells and also shown potent inhibition of DNA topoisomerase I. In HL60 line, 3-O-(E)-p-coumaroyl tormentic acid stimulated apoptotic death of cell mainly through the mitochondrial pathway, considered as key substance for human leukemia therapy [26].

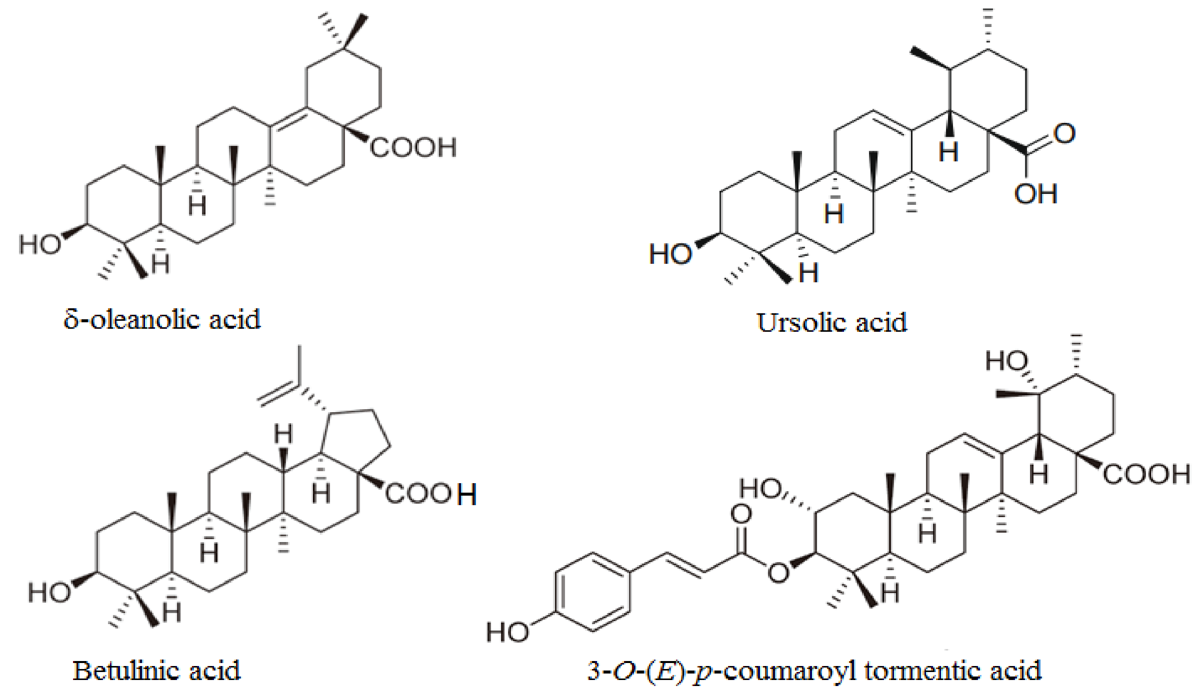

Figure 2. Chemical structures of four triterpenic acids isolated from loquat [26]

In Meth-A-fibrosarcoma-bearing mice, aqueous extracts of loquat (by hot method) also exhibited anticancer effect through immunomodulatory effect, as specified by factors like interleukin-17, interferon-gamma, and *transforming growth factor beta* 1 [9].

The ethyl acetate fraction of leaf [27] and the methanol extracts of seed and leaf of loquat (by maceration, 48h) [28] displayed anti-metastatic effects by suppressing the invasion and migration of B16F10 melanoma cells and MDA-MB-231 human cancer cells of breast that were partly by suppressed the matrix metalloproteinase-9 (MMP-9) and also MMP-2 [27, 28].

2α-hydroxyursolic acid and ursolic acid separated from the ethyl acetate *E. japonica* extracts significantly prevent MMP-9 and MMP-2 effects and considered as key active compounds [27].

The polyphenols such as proanthocyanidins, flavonoids and their glycosides have anticancer effect on human oral tumor cells [10].

Anti-Diabetic activity

The diabetes mellitus known as a metabolic illness with increasing in the blood glucose levels and also characterized by raised the rate of basal metabolism, abnormalities of lipoprotein, high oxidative stress caused injury to beta cells pancreas and trouble in reactive oxygen species (ROS) scavenging enzymes [11,29].

Shafi *et al*. reported (2019) that in streptozotocin induced diabetic rat, the ethanol loquat fruit extract (by maceration, 48h) shown good anti-diabetic effect. [11] The anti-diabetic effect may be related to insulin sensitivity enhancement that will raise tissue glucose uptake or related to induce insulin secretion from the pancreatic beta cells [30]. The flavonoids in the ethanol extract report to have anti-diabetic effect [11].

Combination of summer-harvested leaf of green tea and leaf of loquat produced new fermented tea product. In maltose-loaded Sprague–Dawley rats, this product exhibited reduction of blood levels of glucose and a corresponding decreasing in serum secretion of insulin [31].

Aqueous leaf extracts of loquat led to attenuate the elevation in serum glucose, triglyceride and total cholesterol levels caused by feeding the diet of high cholesterol content in a hypercholesterolemic zebrafish model [32].

The loquat leaf extracts were shown hypoglycemic effects by utilizing the model of high-fat diet-stimulated diabetic C57BL/6J mice [33,34].

Ethanol loquat cell suspension extract (by hot method, 8h) include many pentacyclic terpenoids like corosolic acid, maslinic acid, also ursolic acid, and oleanolic acid. In the high-fat diet mice, administration of such cell suspension cultures of loquat produced the inhibition of the elevation of the blood glucose levels, insulin and leptin levels (34).

In 45% high-fat diet C57BL/6J mice, ethanol leaf extract of loquat containing maslinic acid and corosolic acid (Fig.3) significantly improved the hyperinsulinemia, hyperglycemia, and hyperleptinemia (33).

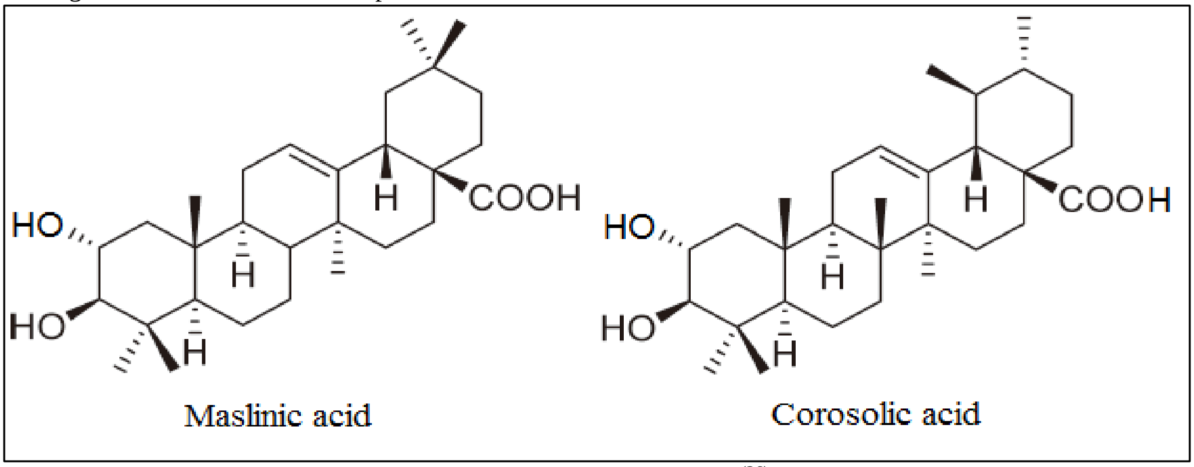

Figure 3. Chemical structures of maslinic acid and corosolic acid (26)

Glucocorticoids are critical metabolic processes regulators involving in gluconeogenesis and increased glucocorticoids level has been accompanied with type2 diabetes, hyperglycemia and resistance of insulin.

11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) stimulates the transformation of 11-ketoglucocorticoids (inactive) into 11β-hydroxyglucocorticoids (active). Therefore, inhibition of such glucocorticoids-activating enzyme is a good curative base for antidiabetic drugs (35,36).

The leaf of loquat preferentially suppressed 11β-HSD1 among 6 traditional hypoglycemic medicinal plants (35). The 2-α hydroxy-3-oxo urs-12-en-28-oic acid, 3-epicorosolic acid methyl ester, tormentic acid methyl ester (Fig.4), corosolic acid (Fig.3), and ursolic acid (Fig.2) are identified as low micromolar 11β-HSD1 inhibitors (36).

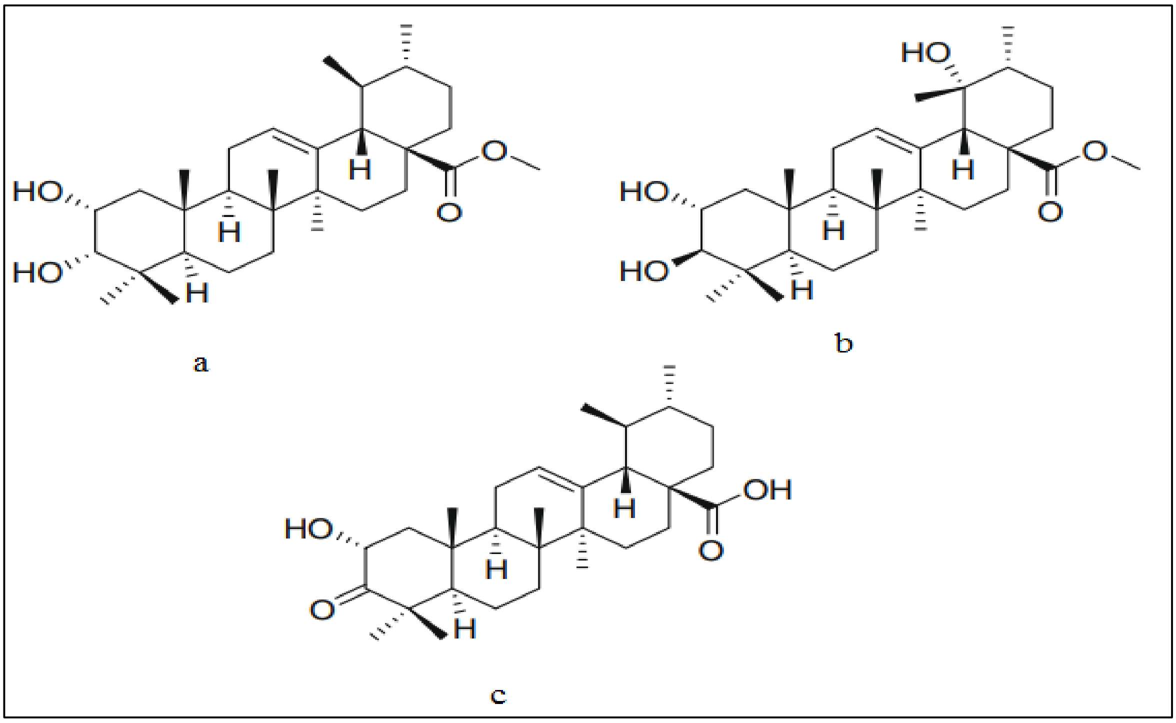

Figure 4. Chemical structures of 3-epicorosolic acid methyl ester (a), tormentic acid methyl ester (b), and 2-α hydroxy-3-oxo urs-12-en-28-oic acid(c) (36)

As for hyperglycemia and its problem, the study revealed the certain plant phenolic compounds that are able to inhibit the digestive enzymes such as α-glucosidase and α-amylase contributory in the carbohydrates breakdown related to the ability of these enzyme to bind to the protein active site [37].

Ahumada *et al*. (2017) reported that both methanol flowers and leaves extracts (by cold method) of *E. japonica* shown inhibitory impact on both enzymes, suggesting a potential hypoglycemia activity, but flowers extract showed the strongest anti-hyperglycemia effect because the levels of flavonoids such as quercetin derivatives and levels of chlorogenic acid (Fig.5) are higher in flowers than leaves [5].

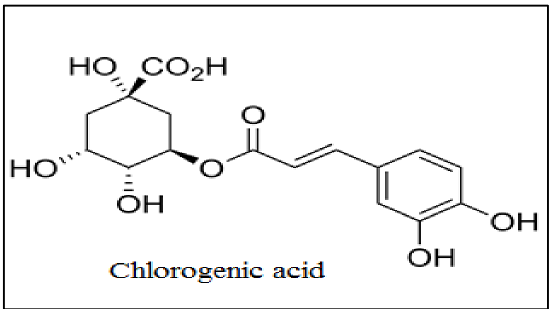

Figure 5. Chemical structure of chlorogenic acid [39]

So the inhibitory effect of these enzymes were directly related to the contents of quercetin derivative and chlorogenic acid and with the antioxidant effect indicated that flowers and leaves have hypoglycemia effect in vitro.

Loquat fruits extract not shown inhibitory impact on α-glucosidase or α-amylase due to the derivatives of quercetin and chlorogenic acid that detected only in flowers and leaves [5].

Toshima *et al.* (2010) reported that fermented tea product shown good inhibitory activity against the α-glucosidase enzyme than that formed from fermented tea leaves only [38].

Oboh *et al.* (2015) exhibited that quercetin derivatives and chlorogenic acid play a significant role on the suppression of α-glucosidase and α-amylase enzymes [39].

Anti-hyperlipidemic activity

Shafi *et al*. (2019) reported that in streptozotocin stimulated diabetic rat, the ethanol fruit extract of *Eriobotrya japonica* (by maceration, 48h) showed the significant hypolipidemic activity [11].

In high-fat diet mice, the cell suspension culture of pentacyclic terpenoids ethanol extracts of loquat exhibited hypolipidemic activity because it decreased white adipose tissue (WAT) weights (include visceral fat, mesenteric, perirenal and epididymal WAT), body weight gain, content of hepatic triacylglycerol and adipocytes size in the visceral depots [33,34].

Fermented tea product (leaves mixture of both green tea (*Camellia sinensis*) and loquat) displayed antiobesity and hypotriacylglycerolemic effects by inhibit the synthesis of hepatic fatty acid and postprandial hypertriacylglycerolemia through pancreatic lipase inhibition [40]. The aqueous extract of leaf of loquat exhibited anti-atherosclerotic effect in a hypercholesterolemic zebrafish model and in cellular assays [32].

Anti-inflammatory activity

The inflammation is a first system of physiological defense and induced macrophages to generate prostaglandins (PGE2) [41], cytokine, nitric oxide (NO) and pro-inflammatory enzymes like secreted phospholipase A2 [42] that stimulate the membrane phospholipids hydrolysis to produce lysophospholipids and free arachidonic acid. The secreted phospholipase A2 group IIA has been firstly found in patients with rheumatoid arthritis in synovial fluid [43] and play a role in inflammatory process [44]. Many inhibitors of phospholipases A2 have been found out and confirmed as a therapy of inflammatory disorders [45].

Maher *et al.* study (2015) reported the ethyl acetate -ethanol (1/2) extract and the dichloromethane-methanol (0:1) fraction of loquat suppressed the pig secreted phospholipase A2 group IB (pG-IB) and the human secreted phospholipase A2 group IIA (hG-IIA) but CH2Cl2/MeOH 0:1 extract was the better one to suppressed especially hG-IIA related to the existence of flavonoid and phenolic compound [46].

The common experimental model for anti-inflammatory research is lipopolysaccharide (LPS)-stimulated inflammation. The n-butanol fraction of leaves of loquat were demonstrated anti-inflammatory property by inhibited the expression of nitric oxide synthase and production of NO by attenuating the activation of nuclear factor-κB (NF-κB) and also down-regulated cyclooxygenase-2 expression and pro-inflammatory cytokines secretion such as interleukin-6 and tumor necrosis factor-α (TNF-α) in the LPS-activated murine peritoneal macrophage model [47].

Seong *et al* (2019) stated that in lipopolysaccharide-induced RAW 264.7 macrophage cells, the ethanol loquat leaf extract (by reflux, 4h) has demonstrated anti-inflammatory effect by suppressing TNF-α production and NO expression [48].

Zar *et al.* (2013) reported that in lipopolysaccharide-induced RAW 264.7 cells, loquat tea water extract of leaves (by boiling for15minutes at100°C) exerted anti-inflammatory effect via inhibiting PGE2 and COX-2 production that stimulated by lipopolysaccharide by using ELISA and Western blot assay, respectively. The new bioactive phenolic compounds in loquat tea may be responsible for its anti-inflammatory potential [12].

In mice, the triterpenes of methanol extract of loquat leaves (by reflux, 3h) inhibited 12-O-tetradecanocylphorbol-13-acetate-stimulated inflammation **(49).** The total triterpenes decreased the inflammatory cytokines production by suppressing NF-κB stimulation from alveolar macrophages in chronic bronchitis rat model (50)**.**

The another model that is utilized to estimate the anti-inflammatory property of *Eriobotrya japonica* extract is a mouse paws edema model (51,52)

In the mouse macrophage-like RAW 264.7 cells, loquat tea water extract (by boiling for15 minutes at100°C) shown inhibitory effects on the expression of TNF-α, interleukin-6, nitric synthase, and NO through the downregulation of pathways of the TGF-β-activated kinase-mediated NF-κB and MAPK (51).

The other mechanism of anti-inflammatory properties of loquat might be antioxidant activity. Tormentic acid (Fig.6) of ethanol cell suspension extract of loquat may increase the activities of glutathione peroxidase, *superoxide dismutase* and catalase in the tissue of liver and decreased paw edema of mice (52)

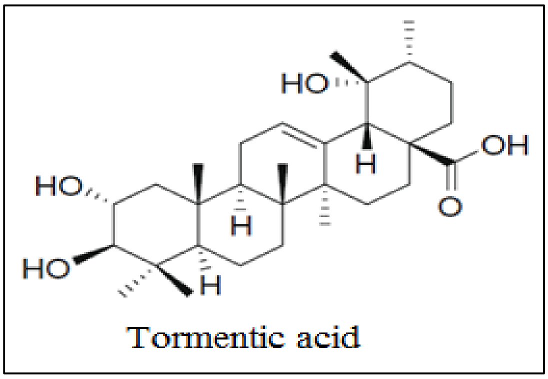

Figure 6. Chemical structure of tormentic acid (36)

In rat ear, by using a model of dinitrofluorobenzene-stimulated allergic dermatitis, ethanol seed extracts (by stirring with mixer, 1week) of *Eriobotrya japonica* also displayed in vivo anti-inflammatory activity and inhibited allergic dermatitis development, where improved Th1/Th2 balance and lower serum levels of immunoglobulin E and thickness of ear were shown (53)**.**

Renal activity

Diabetes mellitus was known as metabolic disease differentiated by hyperglycemia lead up to several complications, such as retinopathy, neuropathy, angiopathy, nephropathy and others (29)**.** Shafi *et al.* (2018) reported that in alloxan-stimulated diabetic rats, ethanolic extract (50%) of seeds and fruits of *Eriobotrya japonica* (by maceration, 48h) displayed renal effect and this effect was evaluated by estimating the tests of kidney function like levels of serum total proteins, creatinine and urea. The result reported that non-significant elevated in serum level of total protein and reduced in levels of serum creatinine and urea. The ethanolic extract of loquat fruits has proper effects on levels of serum glucose (54).

Antitussive and expectorant activity

Wu *et al.* (2018) reported that the ethanol and aqueous extracts of loquat fallen and growing leaves (by hot method, 2h) shown expectorant and antitussive effects. But the ethanol extracts of fallen leaves shown better antitussive effect (relieve cough) that may be related to the higher triterpenoids content of it, like tormentic acid (Fig.6), corosolic acid, maslinic acid (Fig.3), ursolic acid (Fig.2) and other, while aqueous extracts of growing leaves had higher expectorant effect (reduce airway mucus secretion), which may be due to their higher flavonoid content like quercitrin, isoquercitrin, hyperoside, rutin and others (Fig.7) **(55).**

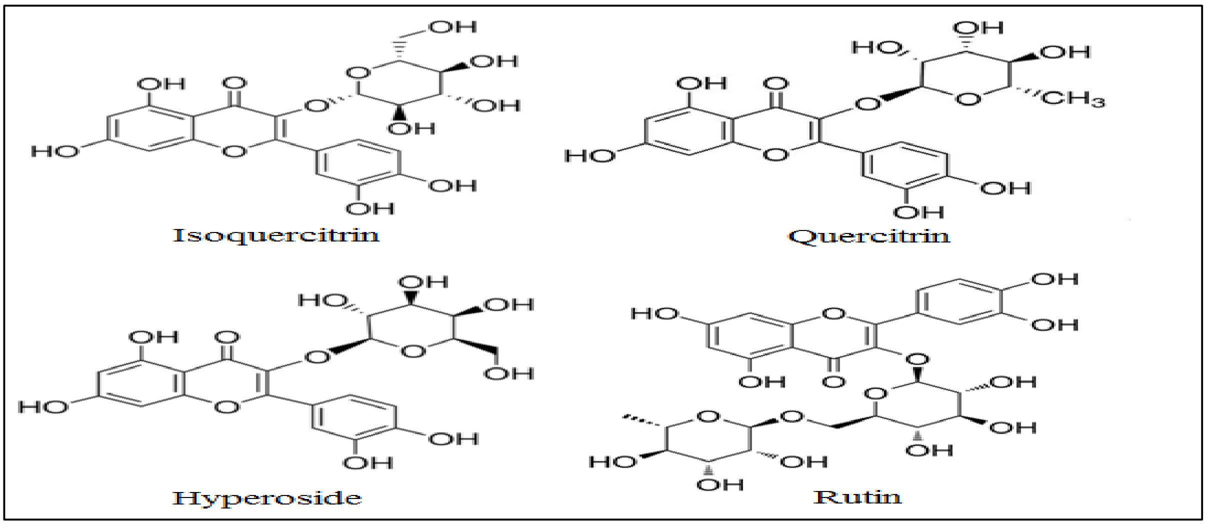

Figure 7. Chemical structures of some flavonoids present in loquat[58]

The major reason of phlegm and coughing, airway mucus hypersecretion, affects the function of lung and closely accompanied with the development and occurrence of chronic inflammation of airway [56].

In the aqueous leaves extract of loquat, some of the identified flavonoids show anti-inflammatory effect via NF-κB and signal transducer and activator of transcription *1* inhibition [57]. NF-κB plays an important role in proinflammatory cytokines production.

In severe cough cases, inflammation is playing an essential role. In eosinophilic bronchitis, an inflammation of lower airway can alleviate sensitivity and severity of cough [59].

The anti-inflammatory activity of loquat triterpenoids might be due to suppressed signal transduction of MAPK [52, 60].

Anti-Melanogenic activity

Seong *et al* (2019) stated that ethanol loquat leaf extract (by reflux, 4h) show anti-melanogenic activity through its anti-inflammatory and anti-oxidant activities. Ethanol extract can protect the skin of human from inflammation and also from oxidative stress, related to the higher content of quercetin (Fig.8) and polyphenol that exhibit the inhibition of melanin synthesis [48].

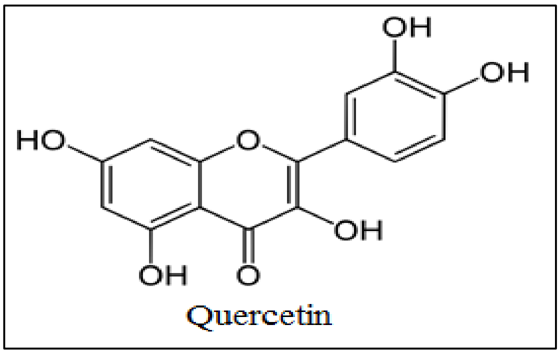

Figure 8. Chemical structure of quercetin [18]

Ethanol extract can regulate production of melanin since melanin plays an important role versus production of UV-stimulated ROS; ethanol extract has shown potent anti-inflammatory and anti-oxidant activities [48,61].

New studies have found that by different inflammatory skin disorders (like dermatitis, eczema), the hyperpigmentation is shown [62, 63].

In B16 melanoma cells, the methanol leaf extract of *Eriobotrya japonica* exerted dose-depending melanogenesis suppression [64]. In addition, 70% and 30% ethanol loquat leaf extracts (by several processes of extraction) inhibited mushroom tyrosinase for whitening effects [65].

Effect on eye and skin

Seong *et al* (2019) stated that ethanol loquat leaf extract (by reflux, 4h) did not exert any irritation or induce toxicity in eye and skin by using animal alternative test like HET-CAM, BCOP assay (irritation test of eye) and RHE model (irritation test of skin) [48]. The aim of HET-CAM test is to recognize agents which induce irritation of conjunctiva and the BCOP test is to recognize substances which induce damage of cornea [66]. Therefore, ethanol extract can be used for skin improvement as a cosmetic ingredient.

Hepatoprotective activity

Shahat *et al* (2018) revealed that the methanol extract (80%) of leaves of loquat and its butanol, aqueous, and ethyl acetate fractions were displayed hepatoprotective activity in rats with carbon tetrachloride ($CCl4$)-induced hepatotoxicity [67].

The methanol extract or its fractions administration of this plant were significantly reduce biochemical parameters levels in rats like aspartate transaminase (AST), gamma-glutamyl transferase, alanine aminotransferase (ALT), bilirubin and alkaline phosphate levels but did not influence lipid profiles [67]. The elevation of these enzyme levels specified the loss function of cell membrane and cellular injury [68].

The methanol extract and its fractions also significantly suppressed the CCl4-stimulated increasing level of Malondialdehyde (MDA) which was proved by decreasing in histopathological injuries [67]. MDA, an important CCl4-induced toxicity indicator in rats, is a final product of peroxidation of lipid in liver [69].

Treatment with CCl4 also increased levels of serum triglyceride, low density lipoprotein, cholesterol and also decreased levels of high density lipoprotein that is inverted the weakness of the ability of the liver cells to convert cholesterol to bile acid for excretion and to metabolize lipids. The fractions and extract of loquat suppressed these effects [67].

On the endoplasmic reticulum, CCl4 induces disassociation and disruption of polyribosomes that leads to reduce biosynthesis of protein [70]. Administration of butanol and ethyl acetate fractions significantly suppressed CCl4-stimulated the depletion of total protein and the reduction levels of nonprotein sulfhydryl groups (NP-SH) , but aqueous fraction and methanol extract administration did not. Butanol and ethylacetate fractions are more effective in the protection from liver damage than aqueous fraction and methanol extract [67].

The hydroalcoholic flower extracts of *E. japonica* (by shaking) shown hepatoprotective activity in mercuric chloride treated rats [71].

By HPLC, phytochemical analysis of hydroalcoholic flower extracts of loquat has indicated that polyphenols like gallic acid (Fig.9) and hesperetin (Fig.10) as main antioxidants are present [71].

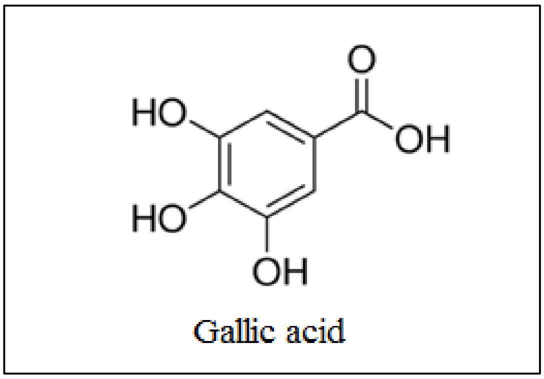

Figure 9. Chemical structure of gallic acid [58]

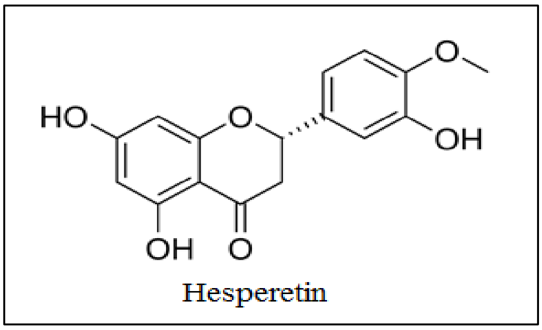

Figure 10.Chemical structure of hesperetin

Long-term alcohol consumption may cause alcohol related hepatic disease development. The ethanol stimulated cytochrome P-450 2E1and cause oxidative stress. The ethanol extracts of loquat leaf (by hot method, 3h) displayed hepatoprotection by reducing the intracellular production of ROS and improving the antioxidant effect in HepG2 cells overproduction cytochrome P-450 2E1. As a result, in manner of concentration-dependent, leaf extract elevated the viability of HepG2 cell and exhibited protective effect in HepG2 cells against ethanol-stimulated toxicity [72].

In rats with non-alcoholic steatohepatitis, ethanol seed extracts of this plant (by stirring with mixer, 7 days) displayed protective effect. The ethanol seed extract (70%) strongly suppressed the elevation in the levels of AST, ALT and fatty droplets forming in the rats liver. The inhibition of fibrosis and fatty liver may result from increasing activity of antioxidant enzyme which may relieve oxidative stresses [73].

Antimicrobial activity

Rashed *et al.* (2014) reported that methanol extract (80%) of stems of loquat (by maceration) was demonstrated antimicrobial effect versus strains of fungi and bacteria related to the presence of triterpenes and flavonoids. It was more effective against Candida albicans indicated that in the treatment of fungal infections, it can be utilized and has no impact on the other strains of fungi and bacteria [18].

Methanol extract of loquat stems due to the presence of flavonoids [74], tannins [75] and also kaempferol 3-O-β-glucoside [76] (Fig.11) which exhibited a good antioxidant and antimicrobial effects.

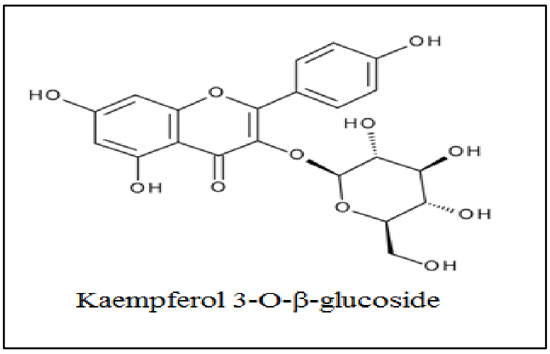

Figure 11. Chemical structure of kaempferol 3-O-β-glucoside [18]

Antiosteoporosis activity

Methanol leaf extract of loquat shows antiosteoporosis effect in the model of ovariectomized mice [77]. Ursolic acid (Fig.2) that isolated from loquat leaves is displayed inhibitory effect on osteoclast differentiation that means inhibited osteoclastogenesis.

The elimination of the multinucleated osteoclasts which contributing to resorption of bone is one of the traditional strategy of osteoporosis treatment. Ursolic acid (Fig.2) suppresses the differentiation of osteoclast via targeting exportin 5 (XPO5) as nuclear exporter protein [78].

Antifibrosis activity

Triterpenic acids of ethanol extract of leaves of loquat (by cold method, 2h) displayed antifibrosis activity via alleviating fibrosis and improving the structure of lung in a rat model of bleomycin-induced pulmonary fibrosis. In the macrophage of alveolar of pulmonary fibrosis, the production of TGF-β1and TNF-α both at the level of mRNA and level of protein were decreased in rats. The triterpene acids such as α-hydroxyoleanolic, euscaphic, arjunic, oleanolic (Fig.12), and ursolic acids (Fig.2) are present in such loquat extracts [79].

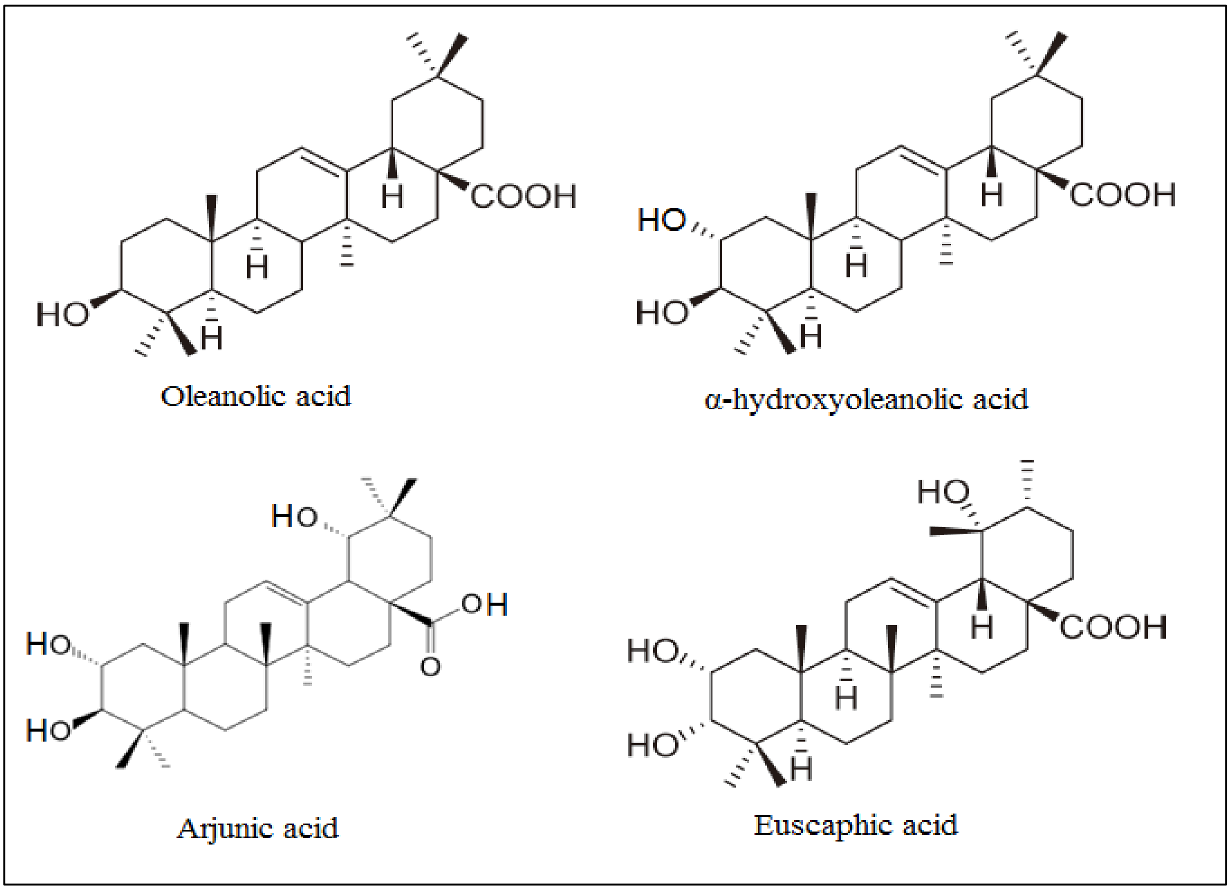

Figure 12.Chemical structures of other triterpene acids present in loquat [26,79]

Antioxidant activity

Bushra Alwash (2017) reported that *E. japonica* fruit juice exhibited antioxidant property by using DPPH assay [2]. The juice plant has ability to scavenge DPPH free radicals by donating their H atom [80,81].

The phenolic compounds especially flavonoids which present in *E. japonica* fruit juice have ability to achieve this reaction [13] and effective as antioxidant rely on position and number of OH groups on the basic flavonoids structure; an antioxidant activity is directly correlated with increasing of hydroxyl groups number [1].

Delfanian *et al* study's (2015) reported the ethanol extract of loquat_pulp and ethanol-water extract of loquat fruit skin (by shaker, 48h at room temperature) shows the higher antioxidant effect in the Rancimat method the β-carotene bleaching and DPPH assay. In stabilization of soybean oil, protective effects of extracts were checking and compared to synthetic antioxidant such as tert-butyl hydroquinone. The treatment of soybean oils with skin extract revealed the strong antioxidant property than the extract of pulp, but soybean oil containing tert-butyl hydroquinone shows the best protection effect. In general, in soybean oil, extracts of fruit pulp and peel displayed good antioxidant effect, so to raise the oil shelf life; these can be used for synthetic antioxidants as a substitute [3].

Few studies reported that this effect of its fruits was related to the existence of cyanidine glycoside, derivatives of benzoic and hydroxycinnamic acids [82].

Ahumada *et al* (2017) revealed that methanol loquat flower and leaf extracts (by cold method) had higher antioxidant effect and also higher total phenolic contents than extract of fruit by using 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid , oxygen radical absorbance capacity (ORAC) and DPPH assay. But the extracts of flower displayed the good antioxidant effect than that of leaves, indicating that the strong antioxidant effect of flowers is directly correlated to their high quercetin derivatives and chlorogenic acid contents. In addition, higher caffeic acid derivatives contents were likely related to higher values of ORAC. Loquat fruits have lower antioxidant and total phenolic contents than leaves and flowers [5].

Rajalakshmi *et al* (2017) stated that methanol fruit and seed extract of loquat (by stirring in shaker, 38h at room temperature) exhibited antioxidant activity by using scavenging action against superoxide free radical. But the methanol extract of *E. japonica* seed shown the highest antiradical activity than the extract of fruit [8].

Maher *et al.* (2015) reported that the ethyl acetate -ethanol (1/2) extract of leaves of loquat displayed an antioxidant effect by using scavenging action against DPPH free radical. But the dichloromethane -methanol (0:1) fraction exhibited a high antioxidant effect and the rich one on phenolic compounds and flavonoids [46]. There is a relation between antioxidant activity and the content of flavonoid and phenolic of loquat extracts that mean these compounds might be contribute for its antioxidant effect [83].

Nawrot-Hadzika *et al.* (2017) reported that the ethyl acetate leaves fraction of loquat (crude extract get by ultrasonic bath at 30°C) shown significant antioxidant effect by phosphomolybdenum, linoleic acid tests and DPPH that mean such extract shown the strongest capability to reduce metal ions, to scavenge DPPH, and to prevent the linoleic acid oxidation.

To localize antioxidants, HPLC-based activity profiling is applying and reported that flavonoid glycosides like isoquercitrin, hyperoside, quercetin-rhamnoside (Fig.7), kaempferol glycosides, cinchonain IIb (Fig.13), and two temporarily specified derivatives of protocatechuic acid (Fig.14), considered as a main compound in charge for good antioxidant effect [20].

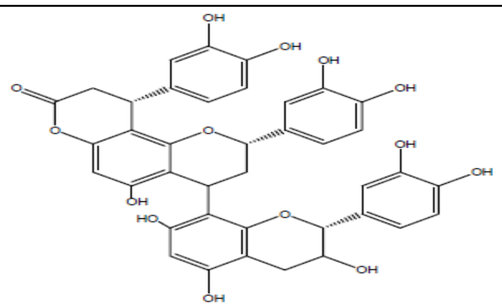

Figure 13.Chemical structure of cinchonain IIb [1]

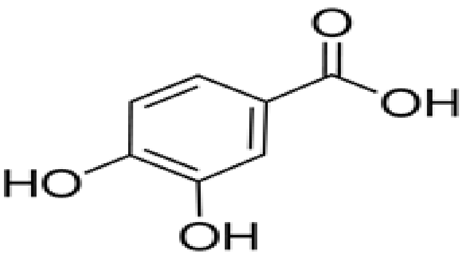

Figure 14. Chemical structure of protocatechuic acid [58]

Zar *et al.* (2013) reported that loquat tea (made from roasted leaves of loquat) shows higher antioxidant effect compared to its fresh leaves by inhibiting cellular ROS and scavenging DPPH. In lipopolysaccharide (LPS)-activated RAW 264.7 cells, loquat tea extract suppressed ROS production. New bioactive phenolic compounds that found in loquat tea are responsible for its antioxidant effects [12].

Seong *et al* (2019) revealed that ethanol loquat leaf extract (by reflux, 4h) displayed good anti-oxidant activity by using ABTS, DPPH and a superoxide dismutase (SOD) assay [48].

Rashed *et al* (2014) stated that methanol stems extract (80%) of loquat (by maceration) was demonstrated the excellent antioxidant effect by the TEAC and ORAC assays related to the presence of active constituents as triterpenes like ursolic (Fig.2), corosolic (Fig.3) and oleanolic acids (Fig.12) and flavonoids like kaempferol 3-O-β-glucoside (Fig.11), quercetin (Fig.8), quercetin 3-O-α-rhamnoside (Fig.7), and naringenin (Fig.15) [18].

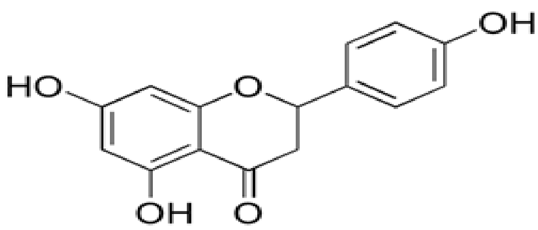

Figure 15. Chemical structure of naringenin [18]

Ursolic acid (Fig.2) that separated from loquat was displayed a strong antioxidant effect and good scavenging activity against DPPH radical at different degrees [84].

Fouedjou *et al.* (2016) reported that methanol extracts (crud extracts) and their fraction (EtOAc and n-BuOH extracts) and compounds that isolated from E. *japonica* stem bark shown antiradical activity by using ferric (Fe3+) reduction antioxidant power, anti-hemolytic and DPPH assays and the most active fraction among them was the EtOAc fraction of E. *japonica*. It can be reported that antioxidant effect increases with the crude extracts fractionation.

Amongst the isolated compounds of *E. japonica*, cinchonain IIb (Fig.13), catechin (Fig.16), lyoniresinol 2-a-O-β-D-xylopyranoside (Fig.17) were identified as the most important antioxidant ones. The antioxidant effect that exhibited by *E. japonica* were related to their high phenolic compounds content [1].

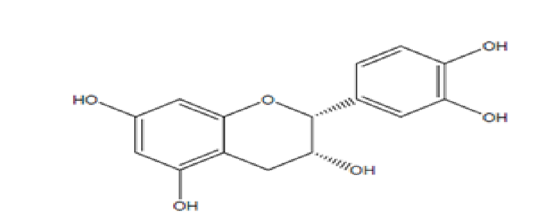

Figure 16. Chemical structure of catechin [1]

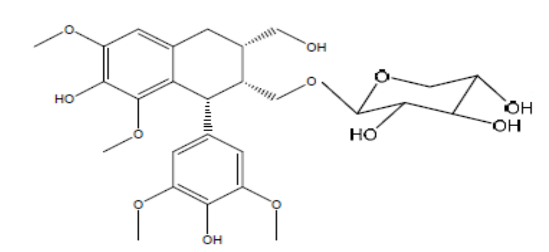

Figure 17. Chemical structure of lyoniresinol 2-a-O-β-D-xylopyranoside [1]

Conclusions

In this review we focused on the main pharmacological activities identified and the main bioactive compounds reported in different parts of loquat. Phytochemical studies with loquat have reported that tannin, quercetin, chlorogenic acid, ursolic acid, oleanolic acid and caffeic acid, consider the major constituents. Different kinds of pharmacological activities have been reported in *Eriobotrya japonica* such as antioxidant, antibacterial, hypolipidemic, anti-diabetic activity and other. For researchers, the wide scope range is available to evaluate and explore the medicinal uses of the drugs.

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