

REVIEW

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The chemical composition and pharmacological activities of *Morinda citrifolia*

Shiyang Zhou^{1,2,3,4,5†} and Gangliang Huang^{1*†}

Abstract

Morinda citrifolia has been widely used by Polynesians as a folk medicine for more than 2000 years. It was reported that the main chemical components of *Morinda citrifolia* include nthaquinones, phenylpropanoids, flavonoids, terpenoids, glycosides, steroids, fatty acids and their esters, etc., it has a wide range of therapeutic properties, including anti-bacterial, anti-oxidant, anti-inflammatory and analgesic, hypoglycemic, hepatoprotective, protective cardiovascular and anti-tumor effects. In order to reveal the nutritional and medicinal value of *Morinda citrifolia* and provide reference for further rational development and comprehensive utilization of *Morinda citrifolia* resources, the chemical composition, pharmacological activity and mechanism of *Morinda citrifolia* were reviewed in this review.

Keywords *Morinda citrifolia*, Chemical composition, Pharmacological activities, Mechanism

Introduction

Morinda citrifolia L. was the Rubiaceae family. It was a perennial evergreen broad-leaved shrub or small tree growing in tropical or subtropical regions [1]. As early as two thousands years ago, the Polynesian indigenous people have made full use of its roots, skins, leaves, stems, flowers and fruits as medicine. It was generally believed that *Morinda citrifolia* has shown better treatment effects in chronic diseases such as arthritis, diabetes, heart disease, high blood pressure, and wound

infections such as knife wounds and gunshot wounds [2]. *Morinda citrifolia* was widely distributed in the South Pacific islands, such as Fiji, Cook, Polynesia, Samoa, Indonesia. In China, it was mainly distributed in Hainan island and Taiwan island [3]. The *Morinda citrifolia* was the fruit of the Noni plant, which in China was called *Morinda citrifolia*, also called girl, Indian mulberry, four seasons fruit. *Morinda citrifolia* has been called “miracle fruit”, “gift from God”, “super fruit”. The magic of *Morinda citrifolia* lies in the first fruit and then flowering, and it was growing while flowering. The *Morinda citrifolia* has more flowers and grows for a long time, and the fruit will not rot for a year, also known as “mummy fruit”. As early as BC, the indigenous peoples of the Pacific islands discovered the natural health and medical effects of *Morinda citrifolia*, they regarded *Morinda citrifolia* as a god. As a gift from God, often fermented *Morinda citrifolia*, and then filtered, as a daily drink and treatment of disease [4]. Although there was no modern medical equipment on the island, the locals have no three heights, no cancer, and a long life expectancy of 82 years, which scientists say may be related to the long diet of *Morinda citrifolia* [5–7].

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In recent years, domestic and foreign scholars have conducted chemical composition studies and found the *Morinda citrifolia* was rich in more than 200 nutrients, mainly containing anthraquinones, phenylpropanoids, flavonoids, terpenoids, glycosides, steroids, fatty acids and their esters, and has pharmacological effects such as anti-bacterial, anti-oxidant, anti-inflammatory and analgesic, hypoglycemic, hepatoprotective, protective cardiovascular and anti-tumor effects (Fig. 1). *Morinda citrifolia* extract was a safe natural antioxidant with antioxidant activity and protection of cardiomyocytes, which can regulate energy metabolism of damaged cardiomyocytes and delay the process of heart failure [8]. The *Morinda citrifolia* could be used as a dietary supplement, it was could also be used as a natural health promotion agent, more and more popular in the world, the market was growing [9]. With the improvement of people's quality of life and the enhancement of health awareness, as well as the various medicinal values and health functions of *Morinda citrifolia* have been gradually confirmed and affirmed. It has quickly become the new favorite of researchers of medicinal plants and health products in the world [10]. It was great practical significance to fully understand the research status of *Morinda citrifolia*. Herein, the chemical composition, pharmacological activity and action mechanism of *Morinda citrifolia* were reviewed.

Chemical constituents

Anthraquinones

Most rubiaceae plants were rich in anthraquinones, and 13 anthraquinones have been isolated from *Morinda citrifolia*. In 2005, Pawlus et al. [11] isolated a large number of anthraquinone compounds from *Morinda citrifolia*, including 2-methoxy-1, 3, 6-trihydroxy-anthraquinone (1), 1, 8-dihydroxy-2-hydroxymethyl-5-methoxy-anthraquinone (2), 1, 3-dihydroxy-2-methoxy-anthraquinone (3), 1, 2-methoxy-anthraquinone. 6-dihydroxy-5-methoxy-2-methylanthraquinone (4), alizarin-1-methyl ether (5). Kim et al. [12] isolated 2-hydroxy-1, 8-dimethoxy-7-methoxy-methylanthraquinone from *Morinda citrifolia* (6). Kamiya et al. [13] isolated 5, 15-*O*-dimethylmorindol (7), anthragallol-1, 3-dimethylether (8), anthragallol-2-methylether (9), 6-hydroxyanthragallol-1, 3-dimethylether (10), morindone-5-methylether (11). Lin et al. [14] obtained 1, 5, 15-*tri-O*-methylmorindol (12), 1, 5, 7-trihydroxy-6-methoxy-2-methoxy-methylanthraquinone (13) from *Morinda citrifolia*. The specific structures of anthraquinones were shown in Table 1.

Phenylpropanoids

Morinda citrifolia contains a variety of phenylpropanoid compounds, including 1 phenylpropionic acid structure, 6 coumarins structure and 25 lignans structure. Phenylpropionic acid compounds basically exist in

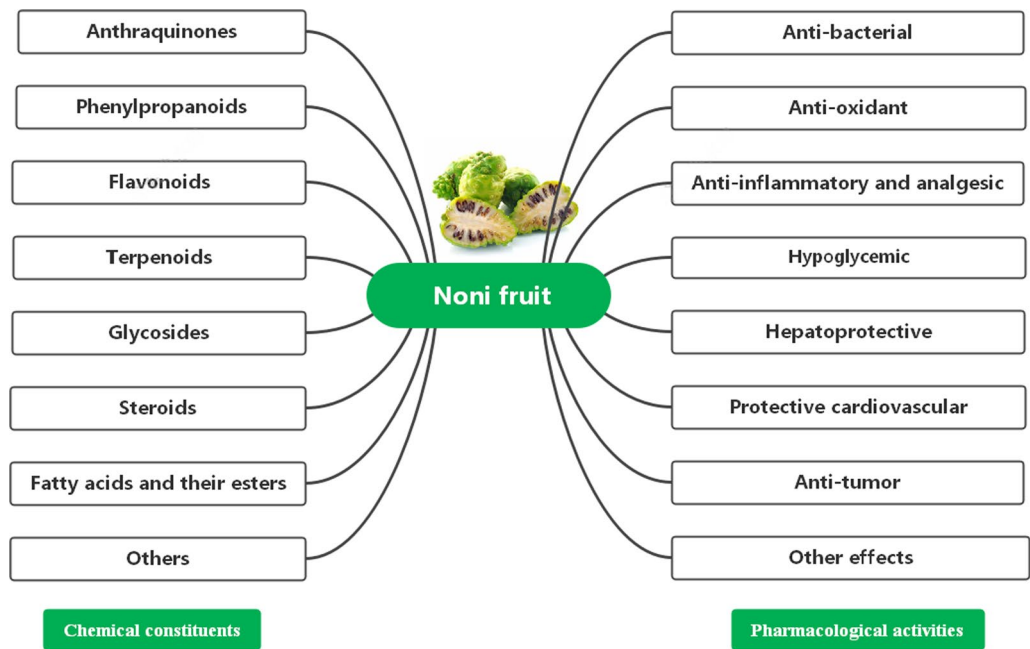
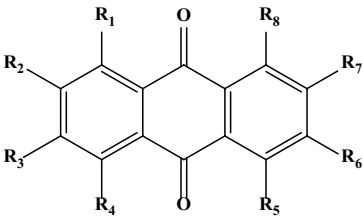


Fig. 1 Chemical composition and pharmacological activity of *Morinda citrifolia*. *Morinda citrifolia* resources

Table 1 Anthraquinone compounds in *Morinda citrifolia*

Compounds	Substituent group								Reference
	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇	R ₈	
1	OH	OCH ₃	OH	H	H	OH	H	H	11
2	OH	CH ₂ OH	H	H	OCH ₃	H	H	OH	11
3	OH	OCH ₃	OH	H	H	H	H	H	11
4	OH	CH ₃	H	H	OCH ₃	OH	H	H	11
5	OCH ₃	OH	H	H	H	H	H	H	11
6	OH	OCH ₃	H	OH	H	H	CH ₃	H	12
7	OH	CH ₂ OCH ₃	H	H	OCH ₃	OH	H	H	13
8	OCH ₃	OH	OCH ₃	H	H	H	H	H	13
9	OH	OCH ₃	OH	H	H	H	H	H	13
10	OCH ₃	OH	OCH ₃	H	H	OH	H	H	13
11	OH	OCH ₃	H	H	OCH ₃	OH	H	H	13
12	OCH ₃	CH ₂ OCH ₃	H	H	OCH ₃	OH	H	H	14
13	OH	CH ₂ OCH ₃	H	H	OH	OCH ₃	OH	H	14



the form of phenolic acid and its derivatives in plants. Pawlus et al. [11] isolated coniferaldehyde from *Morinda citrifolia* (14). At the same time, Pawlus et al. also isolated and identified a coumarin-based compound scopolamine (15). Liu et al. [15] and Deng et al. [16] isolated coumarin compounds including isoscopolamine (16) and 6, 7-dihydroxycoumarin (17) from *Morinda citrifolia*. Liu et al. [17] have isolated coumarin compounds such as aesculin (18) and xeroboside (19) from *Morinda citrifolia*. Bin et al. [18] isolated the coumarin compound nonigly B (20) from *Morinda citrifolia*. A relatively a large number of lignans have been isolated from *Morinda citrifolia* [11, 14, 16, 17, 19, 20], including (-)-3, 4, 3', 4'-tetrahydroxy-9, 7' β -epoxylignano-7 β , 9'-lactone (21), (-)-isolariciresinol 2 α -O- β -D-glucopyranoside (22), (-)-3, 3'-bisdemethylpinoresinol (23), (-)-pinoresinol (24), liriioresinol B (25), liriioresinol B dimethyl ether (26), (+)-3, 4, 3', 4'-tetrahydroxy-9, 7' α -epoxylignano-7 α , 9'-lactone (27), (+)-3, 3'-bisdemethyltanegool (28), (2R, 3S)-2,3-dihydro-2-(4'-hydroxy-3'-methoxy-phenyl)-3-(hydroxymethyl)-7-methoxy-5-benzofuranpropapool-4'-O- β -glucopyranoside (29), (7'E), (7R, 8S)-3, 4, 9-trihydroxy-4', 7-epoxy-8, 3'-oxyneolignan-7'-en-8'-oic acid (30) \cdot (7R, 8S)-3-methoxy-1'-carboxy -4', 7-epoxy-8, 3'-oxyneolignan-4, 9-diol (130), (7R, 8S)-3, 4, 9-trihydroxy-4', 7-epoxy-8,

3'-oxyneolignan-1'-al (31), 3-methoxy-4-hydroxy-5-[(8'S)-3-methoxy-4-hydroxyphenylpropylalcohol]-E-cinnamicalcohol-D-glucopyranoside (32), americanin D (33), balanin (34), americanol A (35), cymbitin A (36), americanoic acid A (37), arteminorin D (38), episesamin 2, 6-dicatechol (39), isoprincepin (40), isoamericanoic acid A (41), morindolin (42), rel-(7 α , 8 β)-3-methoxy-4', 7-epoxy-8, 3'-oxyneolignan-4, 9, 9'-triol (43), drofuran-2(3H)-one (44). The specific structure of phenylpropanoids was shown in Fig. 2.

Flavonoids

Flavonoid widely exists in the plant kingdom, was an important natural organic compound, was also the active component of many plants. So far, 10 flavonoids have been isolated and identified from *Morinda citrifolia*. Including luteolin [15] (45), quercetin [23] (46), kaempferol [16] (47), rutin [21] (48), nicotifloroside [22] (49), daffodil [22] (50), catechin [23] (51), epicatechin [23] (52), naringin [23] (53), hesperidin [24] (54). The specific structure of flavonoids was shown in Fig. 3.

Terpenoids

A total of 25 terpenoids have been isolated and identified from *Morinda citrifolia*, including 13 iridoid terpenoids,

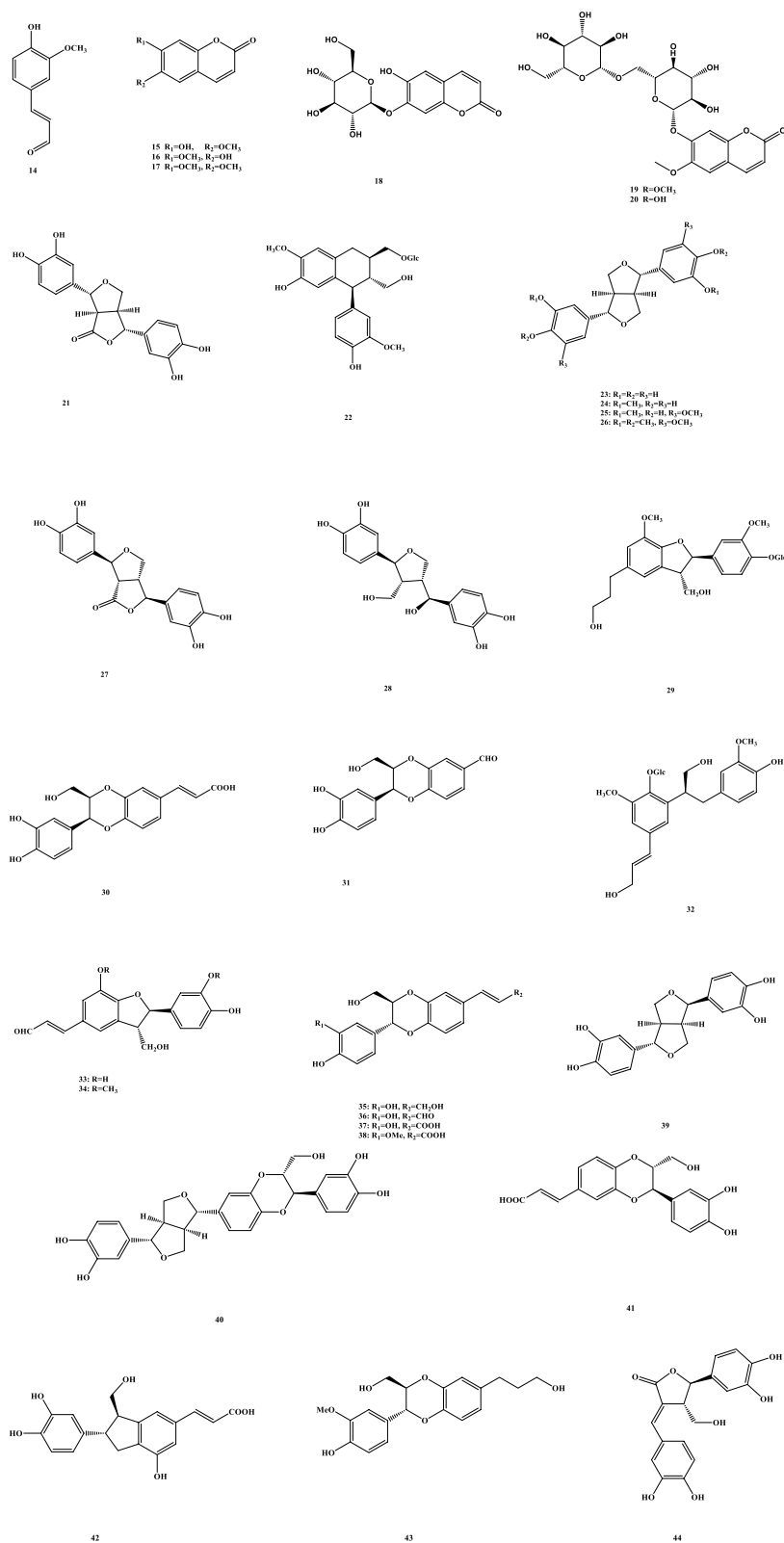


Fig. 2 Structure of phenylpropanoids in *Morinda citrifolia*

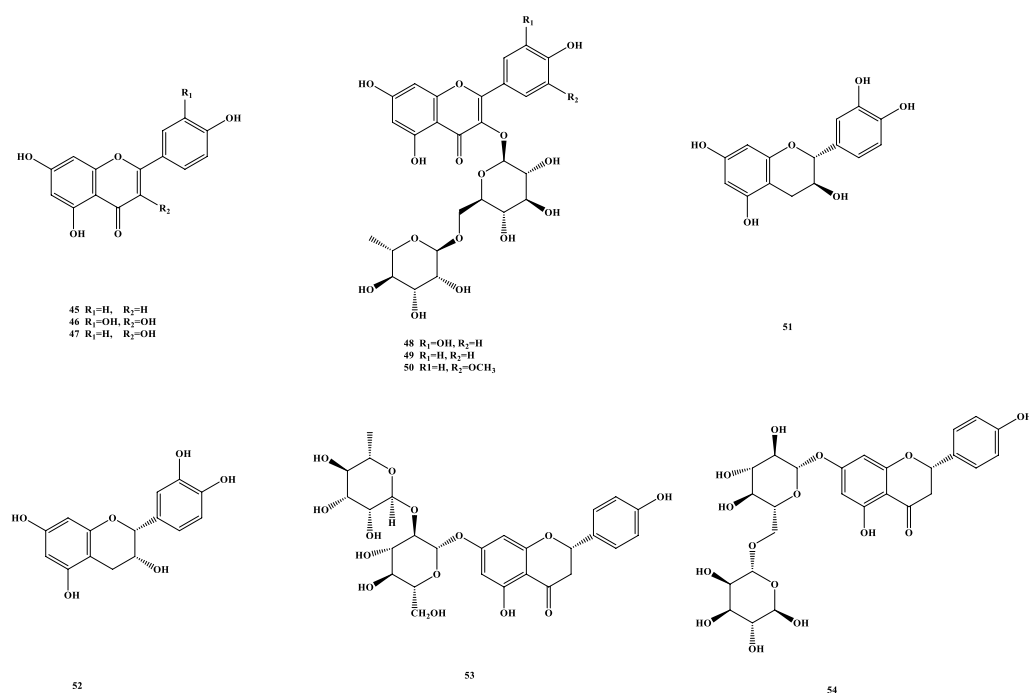


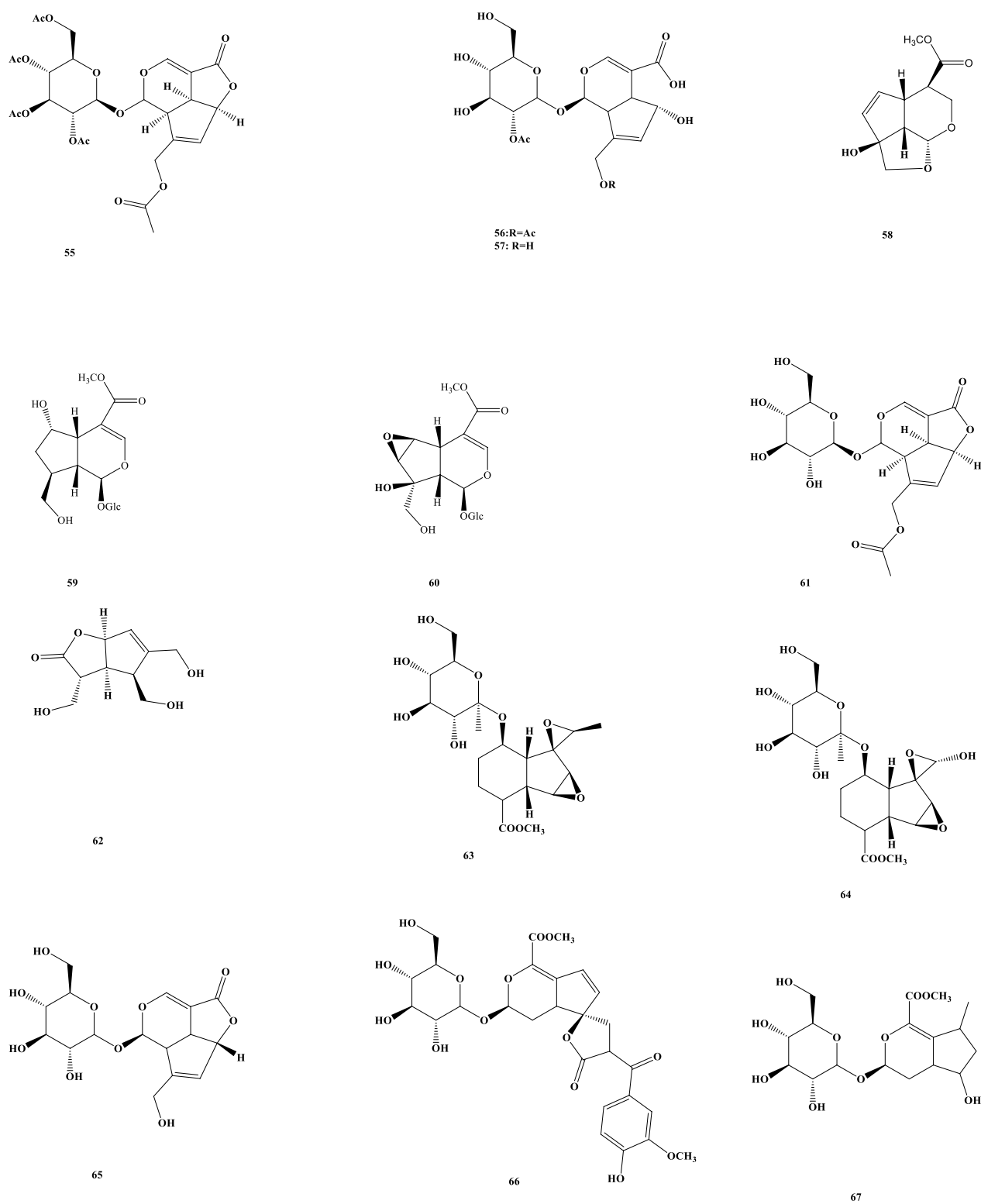
Fig. 3 Structure of flavonoids in *Morinda citrifolia*

1 diterpenoids and 11 triterpenoids. Iridoid compounds in *Morinda citrifolia* were one of the important active substances, mostly in the form of glycosides, and most of them were monoglycosides formed by the combination of C-1 hydroxyl group and glucose. As early as 1979, Levand et al. [25] discovered tetrachloroside (55) from Noni, and later discovered caryophyllic acid [26, 27] (56) and deacetyl-caryophyllic acid [22, 26–28] (57). Tang et al. [29] isolated 4-*epi*-dunnismm from *Morinda citrifolia* (58). Su et al. [30] isolated and identified a variety of iridoid terpenoids from *Morinda citrifolia*. Including 6 α -hydroxyadoxoside (59), 6 β , 7 β -epoxy-8-*epi*-splendoside (60), citrifolmm (61), morinda (62), citrifolmm B epimer a (63), citnfolmm B epimer b (64), deacetylhyaloside (65), dehydromethoxygaertneroside (66), epidihydroconine (67), etc. Samoylenko et al. [26] discovered 4-*epi*euphorbines (68) from *Morinda citrifolia*. Bin et al. [18] isolated nonidoidgly A (69) from *Morinda citrifolia*. So far, only 1 diterpene and 11 triterpene compounds have been found in *Morinda citrifolia*. The diterpenoid compound was phytol [23, 31] (70). Triterpenoids include 1 cycloartenane type tetracyclic triterpene, which was cycloartenol [31] (71). There were three oleanane-type pentacyclic triterpenes, namely hederagenin [30] (72), oleanic acid [30, 31] (73), and fatty acid [32] (74). There were 7 usurane pentacyclic triterpenes, 3-*O*-acetyl pomolic acid [23] (75), equinoxic acid [23, 33] (76), clethricacid [23] (clethricacid, 77),

ferricillic acid [23, 33] (78), ursolic acid [34] (79), ursolactone [33] (80), permolic acid [35] (81). The specific structures of terpenoids was shown in Fig. 4.

Glycosides

Noni contains a large number of glycosides, researchers have found 45 kinds of glycosides. Zhang et al. [36] found glycosidic compounds from *Morinda citrifolia* (*E*-2, 6-dimethyl-6-hydroxyl-oct-2, 7-dienoate-2-*O*- β -*D*-glucopyranosyl- β -*D*-glucopyranoside (82), (2*E*)-oct-enoate-2-*O*- β -*D*-glucopyranosyl- β -*D*-glucopyranoside (83), 3-methyl-2-butenol-*O*- β -*D*-apiofura-nosyl-(1 $\rightarrow$ 6)-*O*- β -*D*-glucopyranosides (84), 3-methyl-but-2-en1-yl- β -*D*-glucopyranosyl-(1 $\rightarrow$ 6)- β -*D*-glucopyranoside (85), benzyl-glucopyranoside (86), hexyl-*O*- β -*D*-glucopyranoside (87), saccharumoside C (88). Su et al. [30] isolated and identified methyl- α -*D*-fructofuran (89), methyl- β -*D*-fructofuran (90), glucose (91) and mannitol (92) from Noni. Subsequently, more and more glycosides were gradually discovered by researchers: (2*E*, 4*E*, 7*Z*)-deca-2, 4, 7-trienoate-2- β -*D*-glucopyranosyl- β -*D*-glucopyranoside (β -*D*-glucopyranose-2-*O*- β -*D*-glucopyranosyl-1-(2*E*, 4*E*, 7*Z*)-2, 4, 7-decatrienoate) [37] (93), 1, 6-di-*O*-octanoyl- β -*D*-glucopyranose [38] (94), 1-*O*-(3'-methyl-but-3'-enyl)- β -*D*-glucopyranose [27, 32] (95), 2-methoxy-4-(2'-hydroxyethyl)-phenol-1- β -*D*-glucopyranoside [17] (96), 2-*O*-(β -*D*-glucopyranosyl)-1-*O*-(2*E*, 4*Z*, 7*Z*)-deca-2, 4,

**Fig. 4** Structure of terpenoids in *Morinda citrifolia*

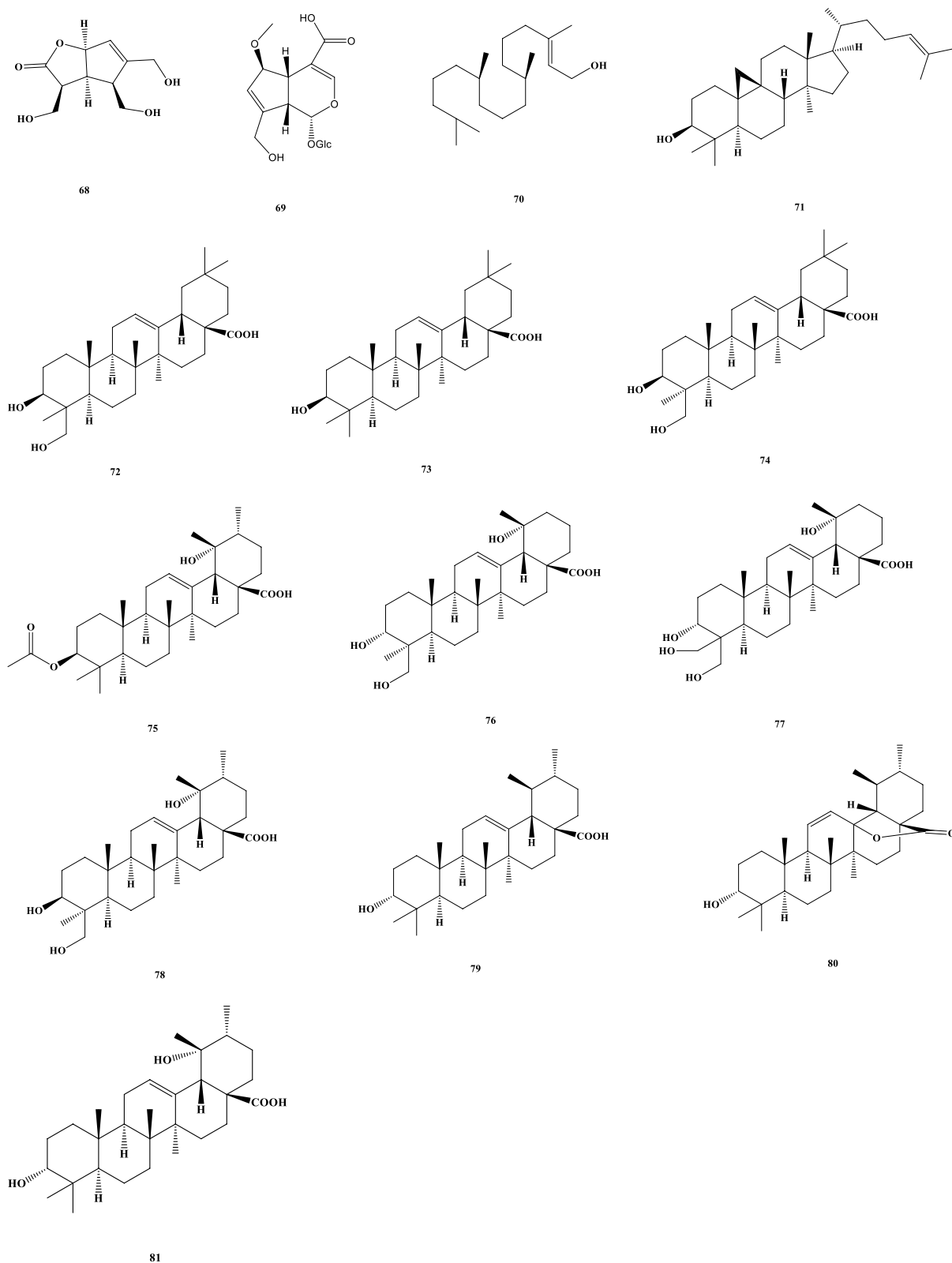


Fig. 4 continued

7-trienoyl- β -D-glucopyranos [39] (97), 2-O-(β -D-glucopyranosyl)-1-O-hexanoyl- β -D-glucopyranose [40] (98), 2-O-(β -D-glucopyranosyl)-1-O-octanoyl- β -D-glucopyranose [40] (99), amyl-1-O- β -D-apiofuranosyl-1,6-O- β -D-glucopyranoside [37] (100), *n*-butyl- β -D-glucopyranoside [32] (101), canthoside A [17] (102), icariin D₂ [17] (103), nonioside A-R [22, 27, 41, 42, 42, 43] (104–121), vanillate glucoside [23] (122), vanillate glucoside [32] (123), β -D-glucopyranose pentaacetate [44] (124) (see Fig. 5). The specific structure of glycosides was shown in Fig. 4.

Steroids

Eight steroid compounds have been isolated and identified from *Morinda citrifolia*. They are β -sitosterol [12, 34, 45] (125), stigmasterol [23, 32, 45] (126), stigmasta-4-en-3-one [23] (127), stigmasta-4-22-dien-3-one [23] (128), campesta-5, 7, 22-trien-3 β -ol [23] (129), β -sitosterol 3-O- β -D-glucopyranoside [21] (130), canolasterol [32] (131), (24S)-ergost-7-en-3 β -ol [31] (132). The specific structure of steroid compounds was shown in Fig. 6.

Fatty acids and their esters

At present, five fatty acids have been isolated from *Morinda citrifolia*, namely, caproic acid [44, 45] (133), caprylic acid [44] (134), linoleic acid [45] (135), *cis*-octadeca-9-enoic acid [45] (136) and succinic acid [35] (137). There were 7 fatty acid esters obtained by isolation and identification. methyl succinate [11] (138) and 1-*n*-butyl-4-(5'-formyl-2'-furyl) methyl succinate [26] (139), 1-*n*-butyl-4-methyl-2-hydroxysuccinate [26] (140), 1-*n*-butyl-4-methyl-3-hydroxysuccinate [26] (141), 2, 3-dihydroxypropyl elaidate [26] (142), 4-ethyl-2-hydroxy-succinatet [14] (143), butyl 2-hydroxysuccinatet [32] (144). The specific structures of fatty acids and their esters were shown in Fig. 7.

Others

Morinda citrifolia also contains a variety of phenolic acids and their derivatives: 1-oxo-5, 6-dihydroxy-8-hydroxymethyl-benzofuran [26] (145), gallic acid [24] (146), gentianic acid [24] (147), anisic acid [24] (148), *p*-cresol [14] (149), *p*-hydroxybenzoic acid [14, 24] (150), *p*-hydroxybenzaldehyde [14] (151), 4-hydroxy-3-methoxybenzaldehyde [14] (152), 2, 5-dihydroxy-4-methoxybenzaldehyde [31] (153), vanillin acid [49, 50, 63] (154), vanillin aldehyde [11, 33] (155), dimethyl phthalate [35] (156), 5-hydroxymethyl-2-furfural [26, 32] (157), leucylprolyl [32] (158), cytidine [30] (159), 2, 5-furandimethanol [26] (160), α -tocopherol [45, 46]

(161), nonikojic A [18] (162), nonikojic B [18] (163). The specific structures of other compounds were shown in Fig. 8.

Pharmacological activities

Anti-bacterial

Morinda citrifolia has obvious antibacterial effect, and its antibacterial activity was the first pharmacological activity discovered. Recent studies have found that *Morinda citrifolia* has obvious antibacterial (bacterial and fungal) and anti-inflammatory effects. As early as 1956, Atkinson et al. [28] reported that *Morinda citrifolia* could effectively inhibit the growth of bacteria such as Salmonella, Salmonella typhus, Staphylococcus aureus and Mycobacterium herbacter, and pointed out that some phenolic substances in *Morinda citrifolia*, such as rhizobin, alizarin, anisotin and other anthraquinones, might be responsible. These ingredients have a significant effect on skin infection, cold, fever and other diseases caused by bacteria. West et al. [47] studied the in vitro antibacterial activity of the *n*-butanol extract of the methanol extract of *Morinda citrifolia*, and found that the extract showed a good antibacterial activity against *E. coli*, *S. aureus*, and *C. albicans*. Of the three microorganisms, *C. albicans* appears to be the most sensitive to the antibacterial activity of *Morinda citrifolia* extracts. At 0.8 mg/mL, all *C. albicans* growth was blocked. At the same concentration, the growth of most *E. coli* was inhibited, but complete cessation of growth did not occur until 1.4 mg/mL. The sensitivity of *S. aureus* to the extraction concentration of *Morinda citrifolia* was lower than that of the other two organisms. And further pointed out that the antibacterial activity was related to the cyclic and ugly terpenoid compounds rich in *Morinda citrifolia*, especially the deacetylated glyoxalic acid and glyoxalic acid. Solomon et al. [48] found that ethanol and hexane extracts of *Morinda citrifolia* had anti-tuberculosis efficacy, because these extracts inhibited the growth of 89% to 95% mycobacterium tuberculosis. Further mechanism of action found that *Morinda citrifolia* contains cyanoside and alizarin and other cyclic iridoid glycoside structure compounds, can inhibit some pathogenic strains, such as: *P. aeruginosa*, *S. aureus*, *B. subtilis*, *E. coli*, Salmonella, Shigella, etc., etc. These are also the material basis of *Morinda citrifolia* extract can be used to treat skin infections and other infectious diseases.

Anti-oxidant

Morinda citrifolia has strong antioxidant function, its antioxidant capacity was stronger than common antioxidants, including vitamin C, α -tocopherol, BHA, grape seed powder and so on. *Morinda citrifolia* has



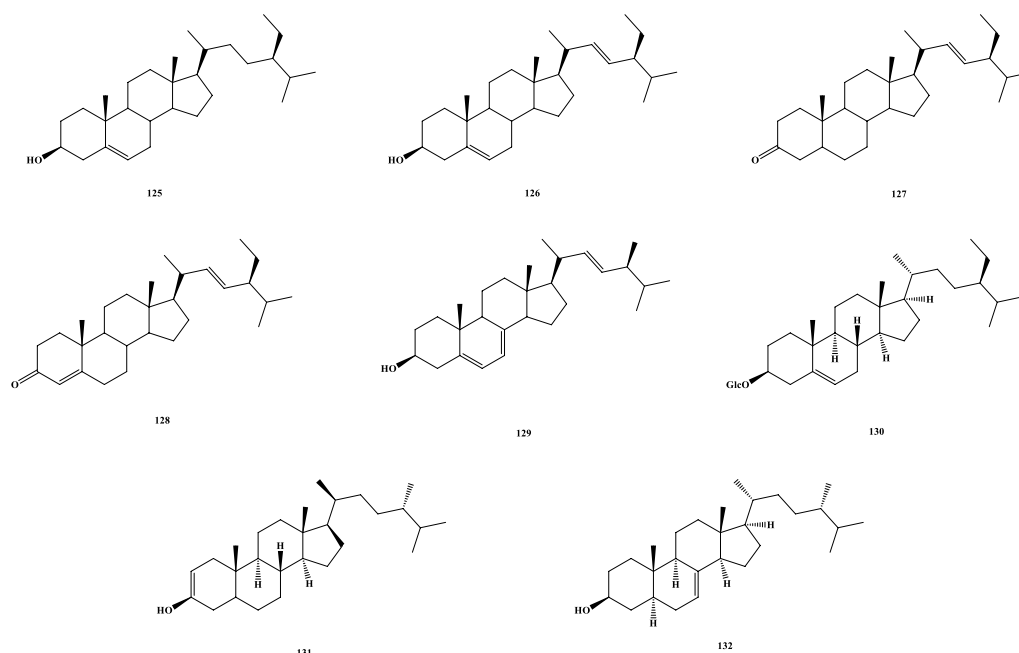


Fig. 6 Structure of steroid compounds in *Morinda citrifolia*

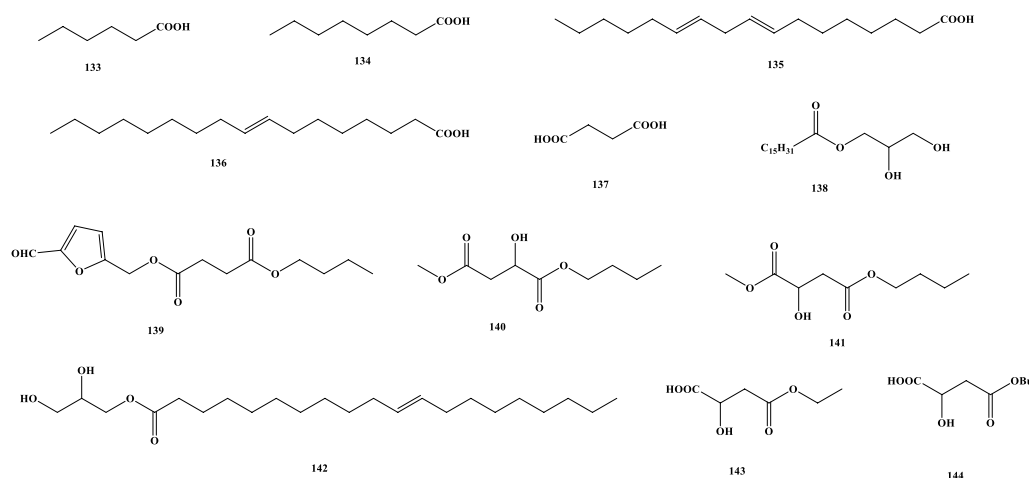


Fig. 7 Fatty acids and their esters in *Morinda citrifolia*

strong free radical scavenging and antioxidant ability. Mhatre et al. [49] compared the contents of methanol extract, water extract and commercial *Morinda citrifolia* and their differences in the scavenging rates of 1, 1-diphenyl-2-trinitrophenylhydrazide free radical (DPPH), superoxide anion and peroxy radical. The results showed that all three extracts had certain antioxidant activity, among which methanol extract had the strongest antioxidant activity, and showed a significant dose–effect relationship with its polyphenols and flavonoids. The results showed that the superoxide

anion scavenging activity of the methanol extract of *Morinda citrifolia* was 33.16 ± 3.8 $\mu\text{g/mL}$ ascorbate equivalent, and the superoxide anion scavenging activity of the water extract of *Morinda citrifolia* was 15.6 ± 2.6 $\mu\text{g/mL}$ ascorbate equivalent. The peroxyradical scavenging activity of *Morinda citrifolia* extract was as following, the ascorbate equivalent of methanol extract was 22 ± 0.17 $\mu\text{g/mL}$, the ascorbate equivalent of water extract was 16.5 ± 0.17 $\mu\text{g/mL}$, and the scavenging activity was 6.12 ± 0.11 $\mu\text{g/mL}$, indicating that the scavenging activity was

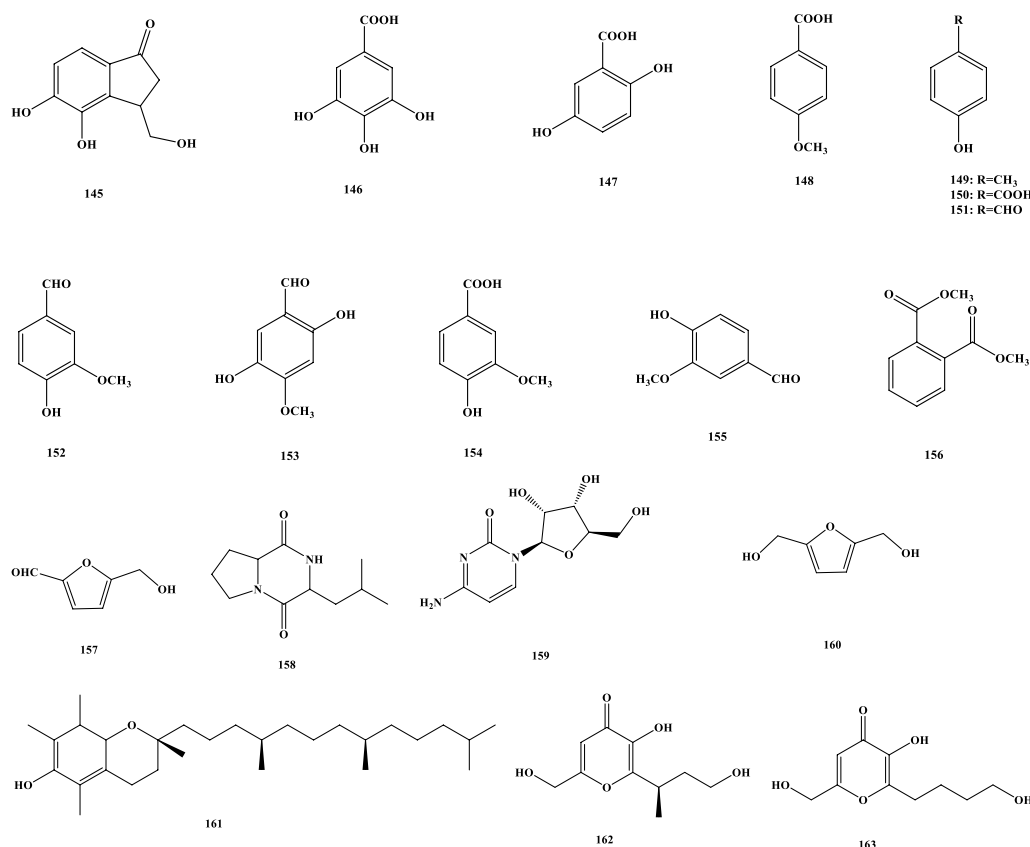


Fig. 8 Structure of other compounds in *Morinda citrifolia*

significant. Mohd et al. [50] tested the antioxidant effects of ethanol extract and ethyl acetate extract of *Morinda citrifolia* by ferric thiocyanate method and thiobarbituric acid experiment. The results showed that compared with α -tocopherol and gallic acid of the same weight, the ethyl acetate extract of *Morinda citrifolia* could effectively inhibit lipid oxidation. Kamiya et al. [51] found through TBARS experiment that methanol extract and ethyl acetate soluble component of *Morinda citrifolia* could significantly inhibit copper ion mediated low-density lipoprotein oxidation, with inhibition rates of 88% and 96%, respectively. Further analysis of its active ingredients revealed six compounds, 3, 3-bisdemethylpinoresinol, americanolA, americanin A, americanoic acid A, morindolin and isoprincepin all inhibit the oxidation of LDL by copper ions in a dose-dependent manner, and their effect was equal to or even stronger than that of the known antioxidants 2, 6-di-tert-butyl-p-cresol [51, 52]. It has been found that the antioxidant activity of these compounds was mainly due to the number of phenolic hydroxyl groups. Since LDL oxidation was an important factor leading to atherosclerosis, *Morinda citrifolia*

was similar to other natural antioxidant substances and can delay the occurrence and development of atherosclerosis through its antioxidant effect, especially by inhibiting LDL oxidation. Lignin was a complex phenolic polymer formed from four alcohol monomers. Their structure was very similar to that of polyphenols, and the antioxidant activity of phenols has been demonstrated. Deng et al. [16] isolated two new lignans and seven known compounds from *Morinda citrifolia*, some of which have been proved to inhibit the activity of lipid oxidase and show weak inhibitory activity on cyclooxygenase-2. The IC₅₀ values of these compounds ranged from 0.43 to 16.5 μ M. Wang et al. [53] evaluated the antioxidant activity of *Morinda citrifolia* juice in vivo with heavy smokers as the study subjects. After taking *Morinda citrifolia* juice for 30 days, the mean plasma peroxide anion number and lipid hydroperoxide level in vivo were decreased. The mean SAR in the 29.5 mL dose group decreased from 0.26 ± 0.14 mmol/mL to 0.19 ± 0.10 mmol/mL, and the mean SAR in the 118 mL dose group decreased from 0.26 ± 0.22 mmol/mL to 0.18 ± 0.11 mmol/mL. LOOH levels decreased from 0.53 ± 0.19 mmol/mL to 0.40 ± 0.10 mmol/mL in

the 29.5 mL dose group and from 0.55 ± 0.21 mmol/mL to 0.40 ± 0.14 mmol/mL in the 118 mL dose group. While the placebo group could not be significantly measured, indicating that *Morinda citrifolia* juice has antioxidant activity in smokers.

Anti-inflammatory and analgesic

Mckoy et al. [54] studied the anti-inflammatory effect of water extract of *Morinda citrifolia* by using bradykinin-induced toe swelling model in rats. The anti-inflammatory effect of the water extract of *Morinda citrifolia* was observed by introducing severe local inflammatory response. The results showed that oral dosage of 200 mg *Morinda citrifolia* aqueous extract (mass concentration 200 mg/mL) can rapidly inhibit the formation of toe edema in mice, and it may be related to the mechanism mediated by B2 receptor. Basar et al. [55] studied the analgesic effect of *Morinda citrifolia* on mice by using the hot plate method, and found that it reduced the pain sensitivity of mice to the same degree as tramadol, a central analgesic drug, and inhibited the release of matrix metalloproteinase-9 (MMP-9) in human monocytes stimulated by lipopolysaccharide (LPS). The effect is comparable to hydrocortisone (1×10^{-5} mol/L). The results showed that *Morinda citrifolia* has a good anti-inflammatory and analgesic effects, can effectively reduce the pain and joint injury caused by arthritis, and has the potential to treat gout and rheumatoid arthritis. *Morinda citrifolia* has anti-inflammatory effects while selectively inhibiting some epoxidase (COX-1, COX-2) activity related to chest, lung and colon cancer cells [56]. The results showed that the IC_{50} of *Morinda citrifolia* extract, Aspirin, Indometacin and Cebrex against COX-1 were 5%, 4.55 mmol/L, 0.01 mmol/L and 1.4 mmol/L, respectively. The IC_{50} of COX-2 was 3.8%, 595 mmol/L, 0.4 mmol/L and 0.47 mmol/L, respectively. The in vitro inhibitory effect of *Morinda citrifolia* on these enzymes was compared with the commercial traditional anti-inflammatory drugs, such as aspirin, indoxin, etc. The results showed that *Morinda citrifolia* can selectively inhibit the activity of COX enzyme in vitro, and has a strong anti-inflammatory effect, and no other side effects. Wang MY et al. [57] found that *Morinda citrifolia* juice has a significant analgesic effect. According to studies, the analgesic effect of *Morinda citrifolia* was 75% of morphine, but its adverse reactions are much smaller than morphine, and it does not form dependence. In addition, *Morinda citrifolia* was fed to female SD rats, and the response of each group to temperature (55 °C) was tested. The results showed that the rats fed *Morinda citrifolia* had longer tolerance time to heat than the control rats, and it was dose-dependent.

Hypoglycemic

Diabetes was a clinical syndrome of glucose metabolism disorder caused by insufficient insulin in the body, the incidence of diabetes was increasing year by year, and the patients tend to be younger, so far there was no radical cure. In recent years, it has been found that *Morinda citrifolia* has significant α -glucosidase inhibitory activity. Studies have shown that gut microbiome imbalance has a profound impact on the occurrence and development of type 2 diabetes, and gut microbiome was considered as a potential target for nutritional intervention or drug treatment of type 2 diabetes. Mahadeva et al. [58] studied the rat model of diabetes induced by streptozomycin (STZ) and found that ethanol extract of *Morinda citrifolia* (300 mg/kg) could restore normal blood glucose, glycated hemoglobin, blood urea and blood creatinine in rats. Significantly reduce the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP), which has great significance in the treatment of diabetes. Wang et al. [59] reported the phenolics with hypoglycemic activity in *Morinda citrifolia*, and found that phenolics in *Morinda citrifolia* significantly improved the hyperglycemia, insulin resistance, oxidative stress and glycolipid metabolism of T2D mice by activating AMPK, thus achieving the effect of lowering blood sugar. The phenolic extracts from *Morinda citrifolia* have significant regulatory effects on glucose and lipid metabolism and intestinal microflora. Nayak et al. [60] reported that fermented juice of Noni had hypoglycemic and hepatoprotective properties in induced diabetic rats. The results showed that fermented juice of Noni had significant hypoglycemic and hepatoprotective activities by evaluating fasting blood glucose, body weight and glycogen content in liver tissue of rats. The results showed that blood glucose levels in both groups were significantly lower, $150 \text{ mg/dl} \pm 15.88$ and $125 \text{ mg/dl} \pm 3.89$, respectively, compared with FBS of $360.0 \text{ mg/dl} \pm 15.81$ in untreated diabetic patients. On day 10 of the experiment, the body mass of diabetic animals decreased (10.2%, 5.11%), and significantly increased (6.0%, 3.0%) on day 20. Histological studies have shown significant steatosis of liver tissue in untreated diabetic animals. Pratibha et al. [61] summarized relevant studies on the hypoglycemic effect of *Morinda citrifolia* and analyzed the related mechanism of hypoglycemic effect of *Morinda citrifolia*.

Hepatoprotective

Toxic hepatitis caused by harmful chemicals from working and living environment, food, drugs and alcoholism may further develop into liver damage such as cirrhosis and liver cancer as chemical liver damage. Studies have shown that *Morinda citrifolia* juice has a certain protective effect on liver injury. By monitoring the contents of

hydroperoxidase, vitamin C, vitamin E, glutathione and the activities of superoxide dismutase, catalase and glutathione peroxidase in the liver of rats, Mahadeva et al. [58] found that the extract of *Morinda citrifolia* had a good antioxidant activity. Good antioxidant capacity may be an important reason for its role in protecting liver. Wang MY et al. [62] found after the experiment that the liver lesions of animals pretreated with 20% *Morinda citrifolia* juice and CCl_4 were significantly reduced. Serum ALT and AST levels in *Morinda citrifolia* juice group were significantly lower than those in placebo group. In a related time-dependent study, pretreatment with CCl_4 and 10% placebo in 12 d female SD rats resulted in cumulative liver lesions for more than 24 h, while pretreatment with 10% *Morinda citrifolia* juice was observed to have a protective effect on the liver. Lin et al. [24] studied the effect of *Morinda citrifolia* on liver, and found that *Morinda citrifolia* could reduce blood lipids in hamsters while increasing the excretion of lipid metabolites and bile acids, and its liver antioxidant capacity was enhanced. At the same time, the expression of nitric oxide synthase (iNOS), COX-2, tumor necrosis factor- α (TNF- α), interleukin-10 (IL-10), the enzymolysis level of MMP-9 and the level of ALT in serum can be decreased. Therefore, the liver protection effect of *Morinda citrifolia* was mainly realized by its antioxidant activity and anti-inflammatory effect.

Protective cardiovascular

Low density lipoprotein (LDL) oxidation was an important factor leading to atherosclerosis. Kamiya et al. [51] found through human thiobarbituric acid reactant (TBARS) color development experiment that methanol extract and ethyl acetate extract of *Morinda citrifolia* could significantly inhibit copper ion mediated oxidation of LDL. The results showed that the inhibition rates of methanol extract and ethyl acetate extract were 88% and 96%, respectively. It was concluded that *Morinda citrifolia* can play a role in cardiovascular protection through its antioxidant effect, especially inhibiting LDL oxidation and delaying the occurrence and development of atherosclerosis. The study of Harada S et al. [63, 64] pointed out that the intake of noni juice could reduce the extent of cerebral infarction. The cerebral ischemia-reperfusion model mice were given 10% *Morinda citrifolia* juice freely for 7 d, and the tested indexes showed that *Morinda citrifolia* juice had a protective effect on nerve injury after ischemia. The development of glucose intolerance may be one of the factors that aggravate nerve damage after ischemia. However, it was found that the development of glucose intolerance 1d after ischemia was mainly inhibited by *Morinda*

citrifolia juice in a dose-dependent manner. These results suggest that the protective effect of *Morinda citrifolia* juice may be mediated when ischemic stress-induced glucose intolerance was inhibited. On the other hand, juice intake did not affect the expression of antioxidants, such as copper/zinc superoxide dismutase. The current study suggests that *Morinda citrifolia* juice may have a preventive effect on cerebral ischemia.

Anti-tumor

The anti-tumor effect of *Morinda citrifolia* has long been proved clinically, and the basic research in recent years has provided a solid theoretical and experimental basis for its clinical application. Wang et al. [57] studied the preventive effect of *Morinda citrifolia* in the initial stage of tumor occurrence. Preliminary data show that drinking *Morinda citrifolia* or 1 week can effectively prevent the formation of carcinogens-DNA admixtures. Further exploration of the mechanism of this preventive effect suggests that the antioxidant activity of *Morinda citrifolia* may help to inhibit the formation of carcinogens-DNA adducts, thus achieving the effect of tumor prevention. Hiwasa et al. [65] found that the degree of DNA fragmentation of tumor cells was significantly higher than that of tumor cells treated only with ultra-ultraviolet radiation when Noni juice was added to tumor cells, indicating that *Morinda citrifolia* can induce tumor cell apoptosis. Hornick et al. [66] found that 5% *Morinda citrifolia* can significantly inhibit the formation of new blood vessels in human placental vein grafts, and can effectively slow down the growth and proliferation of newly developed capillaries. When the mass fraction was increased to 10%, blood vessels can degenerate and inhibit angiogenesis in a few days. In addition, 10% Noni juice can also effectively inhibit the formation of human breast cancer transplant capillaries, and make blood vessels degenerate. The results showed that Noni could achieve the purpose of anti-tumor by inhibiting the formation of blood vessels. Hirazumi et al. [67] studied the immunomodulatory function of *Morinda citrifolia* and found that the alcohol-sinking site of *Morinda citrifolia* was composed of rich polysaccharides, which had a good immunomodulatory and anti-tumor effects. In cell model experiments, *Morinda citrifolia* and alcohol sinks stimulate T cells, NK cells, thymus cells and macrophages to produce cytokines, which on the one hand blocks the tumor cell cycle, on the other hand increases the activity of responding cells, thereby indirectly killing tumor cells and preventing the occurrence of other degenerative diseases. Palu et al. [68] showed that *Morinda citrifolia* can enhance the immune activity of mice, and revealed that it regulates the immune system mainly by activating CB2 receptor, and can effectively inhibit interleukin-4

and increase the production of γ -interferon cytokines. The results showed that increasing the concentration of *Morinda citrifolia* extract (1–5 mg/mL) increased CB2 receptor binding/activation by about three times. At the concentration of 1 mg/mL, the binding inhibition rate of *Morinda citrifolia* extract on CB1 receptor was 13%, but the binding/activation rate of CB2 receptor was increased by 132%, a tenfold increase. In addition, it was found that the activity of extracting from *Morinda citrifolia* was mainly concentrated in petroleum ether extract, and the binding activity of CB2 was 25% at 100 μ g/mL concentration.

Other pharmacological activities

In addition to the main role of *Morinda citrifolia* mentioned above, experimental studies on hypertension, diabetes, gout and other aspects have also been reported. The study of Palu A et al. [69] showed that in vitro determination, *Morinda citrifolia* juice inhibited xanthine oxidase (XO) in a concentration-dependent manner, and XO catalyzed the oxidation process of uric acid formation from xanthine and xanthine formation from hypoxanthine. The results showed that *Morinda citrifolia* had a dependent inhibitory effect on XO. The inhibitory effects of 1, 5 and 10 mg/mL *Morinda citrifolia* on XO were 11%, 113% and 148%, respectively, with an IC_{50} of 3.8 mg and an IC_{50} of 2.4 microm for allopurinol. *Morinda citrifolia* concentrate also inhibited XO concentration in vitro, and 1 and 5 mg/mL concentrate inhibited XO concentration by 184% and 159%, respectively. The inhibition rate of 0.1 mg/mL methanol extract on XO in *Morinda citrifolia* extract was 64%. This sheds light on the mechanism by which Noni juice improves gout, a gout disease, by inhibiting the action of the XO enzyme. Horsfall et al. [70] induced diabetes with alloxouracil and evaluated the effect of *Morinda citrifolia* and its combination with insulin on blood sugar. It showed the synergistic effect of *Morinda citrifolia* juice and insulin. After 4 weeks of treatment with insulin and *Morinda citrifolia*, the mean fasting blood glucose was 8.0 ± 0.8 mmol/L, which was lower than 15.4 ± 1.5 mmol/L with *Morinda citrifolia* or 12.9 ± 1.6 mmol/L with insulin alone. Pu et al. [71] evaluated the effect of *Morinda citrifolia* juice on gastrointestinal tract by detecting the amount of radioactive isotopes in the gastrointestinal tract of male rats given *Morinda citrifolia* juice and detecting the level of plasma CCK of male rats. The results showed that through stimulating the secretion of cholecystokinin and activating the CCK1 receptor, Oral *Morinda citrifolia* can inhibit gastric emptiness in male rats. Akihisa et al. [72] extracted a new iridoid glycoside, three new hemiterpene glycosides and two new sugar fatty acid esters from the methanol extract of *Morinda citrifolia*, which also contained 11 known

compounds. By studying the effects of these compounds on B16 melanoma cells induced by α -melanocytes, 13 compounds showed obvious inhibition, which reduced 34%–49% of melanin at 100 mmol/L, and had almost no toxicity to cells. The research results of Kim et al. [73] showed that in the primary culture of normal human fibroblasts, anthraquone extracted from *Morinda citrifolia* can be used as a new candidate anti-wrinkle agent because *Morinda citrifolia* has a strong induction effect on extracellular matrix component synthesis. A preliminary study by Deng et al. [74] showed that the crude methanol extract of *Morinda citrifolia* juice showed obvious affinity with gamma-aminobutyrate A, and there was a competitive ligand that might bind to GABA_A receptors and act as an agonist, thus promoting its anti-anxiety and sedative effects. The experimental results showed that the methanol extract of *Morinda citrifolia* had 75% binding inhibition on the agonist radioligand [³H] muscimol at 100 μ g/mL. In the GABA_A binding experiment, the IC_{50} values of the methanol extract and its BuOH and H₂O fractions were 22.8, 27.2 and 17.1 μ g/mL, respectively.

Action mechanism

Mechanism of hypoglycemic action

At present, due to the rapid synthesis of chemical drugs and good effect, clinical drugs were still mainly used, but in view of the long-term used of diabetes patients, chemical synthetic drugs have certain toxic side effects, long-term use of the stomach and liver of patients with potential danger. Therefore, the natural substances with high efficiency and low toxicity with hypoglycemic activity were gradually favored by researchers and consumers from plants, especially from both medicinal and edible plants. A large number of studies have shown that some plants have good hypoglycemic effect, and the effective components are mainly polysaccharides, polyphenols, alkaloids and saponins according to their chemical structure. Studies have shown that the hypoglycemic mechanism of *Morinda citrifolia* was diverse, mainly through regulating the activity of key enzymes, protecting the structure and function of β -islet cells and regulating signaling pathways. Independent studies have shown that the insulin-mimicking activity of *Morinda citrifolia* extract shows increased glucose uptake in differentiated 3T3-L1 fat cells, but no additional or synergistic effect on insulin-stimulated cells [75]. Similarly, ethanol extract from fermented *Morinda citrifolia* stimulated glucose uptake in muscle tubules in C2C12-derived mice [76]. The effect of C2C12 muscle ducts on glucose uptake is attributed to increased expression of AMP-activated protein kinase (AMPK), a known cellular energy sensor [76]. Overall, the effect of *Morinda citrifolia* or its chemicals on increased glucose

uptake may help improve peripheral insulin resistance, which has also been noted in in vivo studies of HFD-fed obese mice and diabetic KK-Ay/TaJcl mice [76]. However, the effect of *Morinda citrifolia* on PTP1B and AMPK in vivo was unknown. Zhou and Huang [77] reported that polysaccharide isolated from *Morinda citrifolia* can enhance the activities of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT) in serum, liver, kidney and pancreas of STZ-induced diabetic rats, reduce the level of malondialdehyde (MDA), protect and repair β -islet cells (Fig. 9) [78, 79].

Anti-tumor mechanism

Morinda citrifolia extracts inhibit tumor growth through various pathways or mechanisms. High levels of cyclooxygenase 2 (COX-2) were closely related to the occurrence of breast cancer, colorectal cancer and lung cancer [80–85]. Wang et al. [80] found that *Morinda citrifolia* could inhibit the production of COX-2 with small adverse reactions. Currently commonly used non-steroidal anti-inflammatory drugs (NSAIDs) can inhibit COX-1 and COX-2 at the same time. Unlike COX-2, COX-1 protects the stomach lining. Once the action of COX-1 was blocked, it will produce stomach irritation, resulting in gastric ulcer and gastrointestinal bleeding and other

serious adverse reactions. Wang et al. [80] analyzed and compared the inhibitory effect of *Morinda citrifolia* with aspirin, indomethacin and semicoxib on COX and found that, unlike other drugs, *Morinda citrifolia* can selectively inhibit COX-2 without blocking the effect of COX-1 (Fig. 9). Therefore, the adverse effects of *Morinda citrifolia* was less than those of these existing clinical drugs. *Morinda citrifolia* can also inhibit the occurrence and development of tumors by scavenging reactive oxygen species. It has been confirmed that free radicals are one of the main factors that cause tissue oxidative damage and lead to cancer [84]. On the other hand, *Morinda citrifolia* has a significant scavenging function on superoxide anion radicals and lipid peroxides in the body et al. [85]. In addition, *Morinda citrifolia* can also promote the apoptosis of tumor cells, inhibit angiogenesis and inhibit tumor growth.

Anti-oxidant mechanism

Oxidative stress was an important form of stress. It refers to the massive generation of free radicals and related substances inside and outside the cell under some specific conditions, and the antioxidant system of the body cannot clear these free radicals in time, resulting in the accumulation of free radicals, which leads to the imbalance of

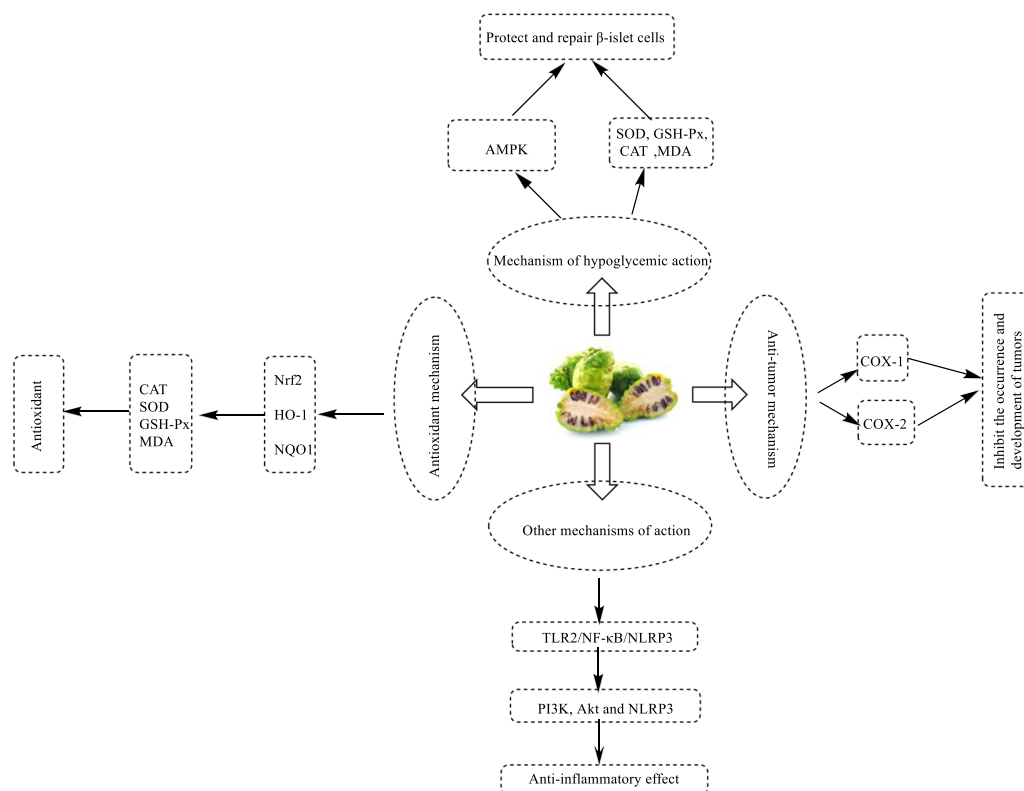


Fig. 9 Action mechanism of *Morinda citrifolia*

the dynamic balance of oxidation and reduction system in the body, resulting in oxidative damage. Under oxidative stress, the polyunsaturated fatty acids that constitute the cell membrane are oxidized, resulting in damage to the structure and functional integrity of the cell membrane, oxidative damage to proteins and nucleic acids, resulting in cytotoxicity and genotoxicity, and changes in enzyme activity, which makes the function of the tissue unable to be realized normally, the immune capacity of the body was reduced, and various diseases are induced. Zhou and Huang [77] analyzed and found that *Morinda citrifolia* polysaccharide had significant regulatory effects on the down-regulation of Nrf2, HO-1 and NQO1 proteins and genes related to oxidative stress signaling pathways in RAW264.7 cells. It can effectively improve the oxidative stress damage of RAW264.7 cells induced by H₂O₂ and inhibit the abnormal decrease of the levels of CAT, SOD, GSH-Px and the abnormal increase of MDA (Fig. 9).

Other mechanisms of action

Osteoporosis was common in diabetic patients over the age of 50, especially over the age of 70. Its mechanisms include primary osteoporosis and secondary osteoporosis caused by diabetes. *Morinda citrifolia* can exert its unique therapeutic effect through nitric oxide, an amazing "information molecule". Nitric oxide has a regulating effect on endocrine, it can regulate the secretion of human estrogen, and has a good effect on inhibiting bone loss. At the same time, *Morinda citrifolia* was rich in vitamin D, which can promote the absorption of calcium in the body. *Morinda citrifolia* can prevent osteoporosis through these two mechanisms of action. In addition, the results showed that *Morinda citrifolia* extract has a significant regulatory effect on TLR2/NF- κ B/NLRP3 signaling pathway, which may be one of the important anti-inflammatory mechanisms. *Morinda citrifolia* extract can effectively regulate the expression of PI3K, Akt and NLRP3 protein, but has no effect on mTOR protein, suggesting that it may protect HUVECs cells by affecting cell survival and apoptosis, rather than regulate the anti-inflammatory effect of NLRP3 through mTOR pathway (Fig. 9).

People's attention to health care was increasing, and the demand for health products. It was becoming more vigorous, and they prefer products of pure natural origin [86]. *Morinda citrifolia* contains rich chemical components and nutrients (including anthraquinones, phenylpropanoids, flavonoids, terpenoids, glycosides, steroids, fatty acids and their esters), and has anti-bacterial, anti-oxidant, anti-inflammatory and analgesic, hypoglycemic, hepatoprotective, protective cardiovascular and anti-tumor effects. It has a good effect on urban diseases

and sub-health in today's society. The global *Morinda citrifolia* related product market was still in its infancy, with few varieties, single functions, and low technical content. In addition to the immunity enhancement involved in the approved *Morinda citrifolia* health food, it also involves the functions of losing weight, protecting blood vessels, promoting blood circulation, regulating menstrual pain, resisting fatigue, and delaying aging. At present, there were more and more in-depth studies on *Morinda citrifolia* in the world, but many of its pharmacological activities only stay in the apparent phenomenon, and the specific mechanism of action needs to be further studied. In addition, for the single components isolated and identified from *Morinda citrifolia*, especially some new compounds, their pharmacological effects need to be further studied to lay a theoretical foundation for developing them into new drugs with independent intellectual property rights. With the more in-depth study on the chemical composition, pharmacological activity and mechanism of *Morinda citrifolia*, the development of its health care and medicinal functions will have a broader space. It will occupy an increasingly important position in the field of medicinal plants and health products in the world.

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