Heliyon 8 (2022) e12039

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Potential metabolites of Arecaceae family for the natural anti-osteoarthritis medicine: A review

Ari Sartinah [a], Ilma Nugrahani [a,*], Slamet Ibrahim [b], Kusnandar Anggadiredja [a]

[a] School of Pharmacy, Bandung Institute of Technology, Bandung 40132, Indonesia
[b] Faculty of Pharmacy, Universitas Jenderal Achmad Yani, Cimahi, Indonesia

ARTICLE INFO

Keywords:
Arecaceae
Primary metabolites
Secondary metabolites
Anti-Osteoarthritis
Anti-inflammatory
Chondroprotective agent

ABSTRACT

Osteoarthritis (OA) is a chronic inflammatory disorder of the joints caused by fluid and cartilage matrix component reduction. This disease results in symptoms of pain, deformity, and limitation of movement. In general, OA is treated with anti-inflammatory drugs and chondroprotection compounds, includes natural nutraceutical ingredients, which are expected to be effective and have minimal side effects. Arecaceae plants are widely spread worldwide, especially in tropical areas. The objective of this review is to collect information about the Arecaceae family as anti-OA agents, with the main study focusing on the primary and secondary metabolites of plants of the Arecaceae family, i.e., sugar palm (*Arenga pinnata*), nipa palm (*Nypa fruticans*), palmyra palm (*Borassus flabellifer*), date palm (*Phoenix dactylifera*), and betel nut (*Areca catechu*) have potential as anti-OA agents. The Arecaceae's metabolites that show anti-inflammatory and chondroprotective effects are galactomannan, fatty acids (linoleic and linolenic acids), flavonoids (quercetin, luteolin, isorhamnetin), phenolics (coumaric acid, ferulic acid), polyphenols (epicatechin), and steroids (stigmasterol, campesterol, spirostane). Based on the reports, the Arecaceae family plants become worthy of being explored and developed into natural anti-OA products, such as supplements or nutraceuticals.

1. Introduction

Osteoarthritis (OA) is a common syndrome that adults worldwide suffer from as a chronic inflammatory disorder in the joints. This disease is caused by the lack of synovial fluid and the components of the cartilage matrix, which impact cartilage damage, pain, deformity, and limited movement [1, 2, 3]. Drugs and nutraceuticals have been widely used to treat this degenerative disorder [4, 5, 6].

OA can generally be treated with anti-inflammatory drugs and chondroprotective agents [7, 8]. An anti-inflammatory drug treats the pain symptoms caused by physical, chemical, and microorganisms stimuli, such as tissue injury, cell death, degeneration, and microbial infection [9, 10]. Anti-inflammatory drugs are divided into two groups, firstly are steroids, such as dexamethasone and prednisone; and the second category is non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, aspirin, diclofenac, and piroxicam [11]. These drugs have been widely utilized, but the side effects accompany the therapy, including gastrointestinal disturbances, cardiovascular risk, and hepatotoxicity [12, 13]. In addition to chemical drugs, various herbal medicines from metabolites of different types of plants have also been used to treat inflammation, such as polysaccharides [14], flavonoids [15], alkaloids [16], terpenoids [17], and steroids [18].

Another treatment for OA is the administration of chondroprotectors, which can protect and repair cartilage tissues [19], *i.e.*, glucosamine and chondroitin [20]. Glucosamine is an amino monosaccharide in the cartilage tissue as a component of glycosaminoglycans (GAGs). Meanwhile, chondroitin is a sulfated GAG composes of branched chains (N-acetylgalactosamine and glucuronic acid) that maintain flexibility, elasticity, and joint maintenance [21]. Several natural compounds, including polysaccharide derivatives, have been reported as potential chondroprotective agents [22].

The natural anti-OA, hyaluronic acid, is also used as a chondroprotector [23, 24] and is a component of joint fluid that functions as a lubricant, free radical scavenger, and in the regulation of cellular activities such as protein binding [25, 26]. Other components of joint fluid are fatty acids, such as linoleic acid, linolenic acid, tetracosadienoic acid, and nervonic acid, which can be used to maintain joint fluid [27]. However, research showed that treatment with hyaluronic acid had controversial results through various clinical practice guidelines and meta-analyses. The integrated meta-analysis and bioinformatics revealed that

* Corresponding author.
E-mail address: ilma_nugrahani@itb.ac.id (I. Nugrahani).

https://doi.org/10.1016/j.heliyon.2022.e12039
Received 16 July 2022; Received in revised form 28 September 2022; Accepted 24 November 2022

hyaluronic acid induces an inflammatory, inhibiting chondrocyte cell regeneration and decreasing anti-OA effectiveness [28]. On the other hand, the study of the efficacy of combination therapy of glucosamine and chondroitin sulfate in patients with osteoarthritis (OA) using a multicenter, randomized, double-blind, and placebo-controlled method proved no significant difference in activity from placebo in terms of reducing joint pain and functional impairment [29]. Therefore, searching for safer and more potent natural anti-OA drugs is necessary.

One type of flora widely spread in the archipelago is the Arecaceae/Palmae family [30]. Some plants from this family, namely sugar palm (*Arenga pinnata*) and palmyra palm (*Borassus flabellifer*) have reportedly been used empirically and scientifically proven to treat OA because they contain polysaccharides as chondroprotectors [31, 32]. Both plants have also been reported to produce various anti-inflammatory secondary metabolites, such as flavonoids, alkaloids, steroids, and phenolic compounds [33, 34]. Economically, the development of natural medicines from plants of the Arecaceae family can provide advantages over existing anti-osteoarthritis drugs, supported by abundant natural resources. They are safe food ingredients with side effects and low toxicity [30]. Therefore, searching for the Arecaceae family plants and their metabolites is interesting to study and develop for alternative natural anti-OA therapy.

So far, no reviews have explained the Arecaceae family's role as a natural source of anti-OA. This article aimed to collect and discuss the reports about anti-OA from the Arecaceae plants during the last two decades, including the primary and secondary metabolites from the Arecaceae family that have anti-OA potential effects.

2. Overview of osteoarthritis (OA)

OA is a chronic inflammation of the joints due to cartilage damage and results in pain, deformity, instability, and limited movement symptoms [35]. OA is characterized by cartilage degradation, osteophyte formation, synovitis, and sclerosis [36]. Cartilage is a flexible connective tissue located at the ends of long bones, whose primary function is to facilitate the transmission of loads with a low coefficient of friction. Cartilage cells (chondrocytes) are composed of a matrix consisting of protein and water. Collagen proteins are embedded in a matrix linked by proteoglycans and glycosaminoglycans (GAGs). These protein compounds form a networked, flexible, and elastic structure with the GAGs that distinguish them from hard bone [37].

OA occurs due to changes in the metabolism of joint cartilage, which are caused by enzyme activity increase that damages the macromolecules of the joint cartilage matrix and decreases the synthesis of proteoglycans and collagen [38]. In the degeneration process, joint cartilage will produce substances that can cause an inflammatory reaction, which stimulates macrophages to produce interleukin (IL)-1β, thereby increasing proteolytic enzymes for extracellular matrix degradation. Changes in proteoglycans result in the cartilage having a high resistance to withstand pressure forces from the joint and other influences that can overload the joint. Furthermore, osteophytes will form at the edges of the joints against the damaged cartilage [39].

Osteophyte formation is a physiological response to repair and reshape joints. By increasing the joint surface area to accept the load, osteophytes are expected to improve the initial cartilage changes in OA. Over time, there is progressive erosion, which also causes the underlying bone to erode [40]. The pressure that exceeds the biomechanical strength of the bone will cause the subchondral bone to respond by increasing cellularity and vascularity so that the bone becomes thick and dense. This process, known as eburnation, results in sclerosis of the subchondral bone. Joint cartilage wears out, breaks down, and causes the symptoms of OA [41].

Globally, the prevalence of radiographically confirmed knee OA in 2010 was estimated at 3.8%. In Southeast Asia, the prevalence of knee OA was 2.2% in men and 3.8% in women [42], while Indonesia had a round of 6.13% for men and 8.46% for women [43].

2.1. Pathophysiology of OA

Osteoarthritis is known as a degenerative disease of cartilage. However, several studies have shown that several factors cause OA, such as trauma, mechanics, inflammation, biochemical reactions, and metabolic disorders [44]. Cartilage tissue lacks blood vessels and innervation, so it cannot produce inflammation or pain in the early stages of the disease. Therefore, the source of pain mainly comes from changes in the non-cartilage components of the joint, such as the joint capsule, synovium, subchondral bone, ligaments, and periarticular muscles. As the disease progresses, changes in bone structure, osteophyte formation, periarticular muscle weakness, ligament laxity, and synovial effusion occur [45].

In OA, the synovial fluid contains several inflammatory mediators, including plasma proteins (C-reactive protein), prostaglandins (PGE2), leukotrienes (LKB4), cytokines (TNF, IL-1β), growth factors, and nitric oxide. These components can induce matrix metalloproteinases and other hydrolytic enzymes (including cyclooxygenase-2 and prostaglandin E), resulting in proteoglycan and collagen breakdown [46]. Recent studies have shown that several signaling pathways involved in OA pathology are Wnt/-catenin, TGF-β and BMP, FGF, NF-κB, and Notch. Their alteration leads to pathological changes in cartilage tissue [47].

Natural compounds such as flavonoids, fatty acids, steroids, and others have promising potential in developing anti-OA drugs [48]. Flavonoids significantly decreased IL-1β stimulated pro-inflammatory mediators in OA-induced mice by inhibiting the NF-kB pathway and also enhanced the repair of damaged cartilage considerably by reducing serum concentrations of metalloproteinase-3 and metalloproteinase-13 (MMP-3 and MMP-13) [49,50]. Similarly, steroids are involved in inhibiting the NF-kB route [51]. At the same time, unsaturated fatty acids reduce the expression of cartilage-degrading enzymes metalloproteinase-MMP-13 and metalloprotease with thrombospondin-5 (ADAMTS-5), oxidative stress, and apoptosis via nuclear factor kappa-betta (NF-kβ) and inducible nitric oxide synthase (iNOS) pathways [52].

2.2. Management of OA

There are some physical and medical procedures to treat OA as follows.

2.2.1. Care

Physically, some efforts are made to care for OA, including:

- Reducing body weight. Weight loss is one of the efforts to treat OA by decreasing joint load. The target body mass index (BMI) is around 18.5–25. Excessive BMI causes a large joint load, increasing joint pressure and accelerating joint damage [53].
- Physiotherapy and rehabilitation to relieve pain and maintain muscle strength and range of motion (ROM). The recommended exercises are ROM exercises for jointment and isometric exercises to help build the supporting muscles. Isotonic exercises should not be done with resistance because they can worsen the disease [54].
- Compressing the OA joint with warm water. Heat therapy reduces pain, muscle spasms, and stiffnes, and increases tendon extensibility [55].

2.2.2. Medical treatment

The medical treatment is divided into modern and traditional medicines usage, as follows.

2.2.2.1. Modern medicines.

- Anti-inflammatory agent

Inflammation is the body tissues responding to the presence of infection, and physical -chemical stimuli [56]. It generally occurs when

microorganisms (bacteria, viruses, or fungi) invade the body, reside in specific tissues, or circulate in the blood. Inflammation can also occur in response to tissue injury, cell death, cancer, ischemia, and degeneration [57]. The inflammatory process is mediated by histamine, prostaglandins, eicosanoids, leukotrienes, cytokines, nitric oxide, and others [58]. It begins with tissue damage due to a stimulus that causes mast cell rupture, followed by the release of inflammatory mediators, then vasodilation occurs, which causes leukocyte cell migration [59].

The anti-inflammatory drugs are divided into steroids and NSAIDs [60]. The first group works by inhibiting phospholipase, which produces arachidonic acid, and produces prostaglandins as inflammatory mediators. Examples of steroids include dexamethasone, prednisone, and betamethasone. Meanwhile, NSAIDs work by inhibiting the cyclooxygenase enzyme and are used to treat patients suffering from pain and inflammatory conditions such as chronic pain, rheumatoid arthritis, and OA. NSAIDs are ibuprofen, aspirin, diclofenac, and piroxicam [61].

- Chondroprotective agents

Drugs that can repair or maintain joint cartilage in OA patients are named chondroprotective agents, including glucosamine and chondroitin [62, 63]. Glucosamine is an amino monosaccharide also found in cartilage tissue as a component of GAGs. At the same time, chondroitin is a sulfated-GAG composed of branched chains (N-acetyl galactosamine and glucuronic acid) that maintain flexibility, elasticity, and joint maintenance. Administration of glucosamine and chondroitin reduces cartilage degeneration. Besides, these compounds have antioxidant activity and protective effects on human chondrocytes by reducing nitric oxide synthase expression and activity, thereby reducing oxidative stress [64].

In addition to those compounds, a substance that is often used as a chondroprotective agent is hyaluronic acid [65]. Hyaluronic acid is a polysaccharide-derived compound consisting of N-acetyl-glucosamine and D-glucuronic acid residues connected by (1–4) and (1–3) bonds. In OA patients, endogenous hyaluronic acid in the joints is depolymerized so that it becomes a lower molecular weight, resulting in cartilage with reduced mechanical and viscoelastic properties [66]. The administration of exogenous hyaluronic acid has been used clinically to reduce the effects of endogenous hyaluronic acid depolymerization in OA patients [67]. Hyaluronic acid is administered to OA patients in two ways: orally and by local injection [68].

2.2.2.2. Traditional medicines. Due to almost all adults suffer OA, empirical herbal medicines have been used for a long time. Specifically, the following sections will explore the literature related to several plant sources of the Aceraceae, as the extensive plant family growing well in tropical areas with potential anti-OA therapies. Many reports explain that they have anti-inflammatory and chondroprotective effects. For example, the sugar palm fruit (*Arenga pinnata*) has been used as an anti-OA treatment [31], and several other Arecaceae family plants, such as have a potential anti-OA effect, including the palmyra palm, nipa palm, date palm, and betel nut [32, 69, 70, 71].

3. Arecaceae and its potential as a source of natural anti-OA compounds

3.1. Sugar palm (Arenga pinnata)

The sugar palm plant is a member of the Arecaceae family that is used by the community for almost all parts, such as fruit, sap, fibers, stems, and leaves. The sugar palm fruit pulp has empirically been used to treat OA [72]. Research by Li *et al.* showed that the ethanolic extract of palm fruit (*A. pinnata*) has anti-inflammatory and antinociceptive activity [73]. Sugar palm fruit also contains polysaccharides, protein, fat, and sera [74], and the ethanol extract of sugar palm fruit contains flavonoids, alkaloids, and quinones [72]. Research shows that sugar palm fruit contains galactomannan polysaccharides, which have an anti-OA effect [75, 76]. The figures of the sugar palm tree (a) and fruits (b) are shown in Figure 1.

3.2. Palmyra palm (Borassus flabellifer)

Just like sugar palm plants, palmyra palms also have many benefits. The fruit's flesh is used as food or in fresh drinks containing galactomannan [78]. Palmyra palm fruit contains fatty acids such as lauric acid, tetradecanoic acid, palmitic acid, palmitoleic acid, octadecanoic acid, oleic acid, linoleic acid, linolenic acid, arachidic acid, and docosanoic acid. Phytochemical screening of this palmyra palm plant shows the presence of polyphenols, alkaloids, steroids, triterpenes, and saponins [79]. Palmyra palm trees have anti-inflammatory activity, with existing research showing that the male flower parts of the lontar plant have anti-inflammatory and anti-arthritis activity. An ethanol extract of male flowers at doses of 200 mg/kg body weight (BW) and 400 mg/kg BW showed significant anti-inflammatory effects and anti-arthritis activity, further confirming the traditional use of the palmyra palm *(B. flabellifer)* in the treatment of inflammation and arthritis. Male flowers contain a steroidal saponin-type spirostane compound with anti-inflammatory activity [80]. The following are Figure 2 the palmyra palm tree (a) and fruits (b).

3.3. Nypa palm (Nypa fruticans)

The nipa palm plant has been used in various traditional medicines in Asia. Several studies related to the nipa palm plant, namely nipa flower stalk extract, have demonstrated its anti-pain and anti-inflammatory activity by suppressing TRPV1 in sciatic nerve injury [82]. The phytochemical content of the nipa palm plant includes phenolics, alkaloids, tannins, flavonoids, terpenoids, steroids, and saponins [83]. Nipa palm sap contains phenolics and flavonoids; the fruit skin contains polyphenols and tannins, and the seeds contain alkaloids [84]. In addition, nipa palm fruit contains polysaccharide (galactomannan), crude fiber, protein, and fatty acid (oleic acid, linoleic acid, linolenic acid, arachidic acid, docosanoic acid, lauric acid, tetradecanoic acid, and octadecanoic acid) [85]. Afterward, the compounds identified in nipa palm fruit flesh are gallic acid, cinnamic acid, chlorogenic acid, protocatechuic acid, hydroxybenzoic acid, quercetin, rutin, and kaempferol [86]. The *Nypa* palm tree (a) and fruits (b) are shown in Figure 3.

3.4. Date palm (Phoenix dactylifera)

Many studies have been carried out on date palm plants regarding OA, including determining the effect of a topical preparation of date palm (*P. dactylifera*) on clinical manifestations of knee OA compared to diclofenac gel. A statistical comparison between the intervention and control groups showed that the dates significantly reduced pain and increased the patient's daily physical activity better than diclofenac gel [88]. Other studies also support that date palm extract has a significant analgesic effect on chronic pain in rats at a dose of 200 mg/kg [89]. This was also confirmed in a study on dates, where as much as 50 mg/kg of the extract was analyzed in a formalin-induced leg edema test in rats. The level of inflammation is detected by measuring the size of the edema, as well as the dose of C-reactive protein (CRP) and the level of homocysteine in the blood. The results showed a very significant reduction in edema size and blood homocysteine levels ($P = .000$) and a significant decrease in CRP values ($P < 0.05$) in the 50 mg/kg extract group compared to the control group, which was 400 mg/kg methionine. The study showed that the extract group had sufficient potential to reduce inflammation *in vivo* [90].

Date palm fruit contains flavonoids such as luteolin, methyl luteolin, quercetin, methyl quercetin, catechins, epicatechins, cinnamic acid, ferulic acid, sinapic acid, coumaric acid and its derivatives, 5-caffeoyl shikimic acid or dactyliferic acid, protocatechuic acid, caffeic acid, syringic acid, p-coumaric acid, ferulic acid, and o-coumaric acid; steroid groups such as cholesterol, stigmasterol, campesterol, and sitosterol; enzymes such as phytase, invertase, and peroxidase; and carbohydrates such as glucose, fructose, mannose, maltose, sucrose, starch, and cellulose. Those

Figure 1. (a) Sugar palm tree; (b) sugar palm fruits [77].

Figure 2. (a) Palmyra palm tree; (b) palmyra palm fruits [81].

metabolites have been known as functional nutrition and herbal medicine components [91]. Below are Figure 4 date palms tree (a) and fruits (b).

3.5. Betel nut (*Areca catechu*)

Betel nut (*Areca catechu*) is a plant of the Arecaceae family that has been a source of herbal medicine for a long time. The study showed the inhibition effect of an ethanol extract of betel nut on lipopolysaccharide (LPS)-induced inflammation. It indicated that the extract has a significant anti-inflammatory effect by decreasing NO and the expression of iNOS and COX-2 [93].

Furthermore, other studies also support the anti-inflammatory effect of this plant; for example, the ethanolic extract of betel nut at doses of 1 and 10 mg/kg/day per oral for five days suppressed carrageenan-induced inflammation in rats by decreasing edema and prostaglandin E2 levels [94]. Some literature shows that betel nut contains polyphenols, alkaloids, starch, and fat. Here are some of the compounds that have been isolated from the betel nut; polyphenols (leukocyanidin, epicatechin, and catechin), flavonoids (luteolin, quercetin, isorhamnetin), alkaloids (arecoline, aracaidine, guvacoline), tannin (proanthocyanidin), and fatty acids (linoleic acid, myristic acid, lauric acid, oleic acid, decanoic, acid, dodecenoic acid, tetradecenoic acid and hexadecenoic acid [95, 96, 97, 98, 99]. Due to the many contents in the nut, some activities, including anti-OA, become rational and make sense. The betel nut tree (a) and fruits (b) are shown in Figure 5.

3.6. Sago (*metroxylon sagu*)

Sago is generally used as a food because it contains starch polysaccharides. In addition, sago also contains non-starch carbohydrates consisting of arabinose, galactose, and rhamnose [101]. Screening on sago fruit contains flavonoids and tannins, which have potential as an anti-inflammatory agent [102]. The sago tree (a) and fruits (b) are shown in Figure 6.

4. Primary and secondary metabolites in arecaceae as potential anti-OA

4.1. Polysaccharides

One of the polysaccharides found in Arecaceae plants is a galactomannan, with the structure shown in Figure 7. This compound is in

Figure 3. (a) *Nypa* palm tree; (b) nypa palm fruits [87].

the flesh of sugar palm fruit, palmyra palm fruit, and nipa palm fruit. Structurally, galactomannan consists of mannose and galactose chains, formed from -(1–4)-D-mannose as the main chain, with one branched unit of -D-galactose attached to the -(1–6) position [104].

Galactomannan has an anti-OA effect, with a recent study in rats showing that it decreased the rate of joint damage and pain induced by OA. In this study, sodium monoiodoacetate was administered to rats (OA group, 1 mg/25 L) at the right tibiotarsal joint, and galactomannan *Delonix regia* (30–300 g) was administered by the intra-articular route on days 14 and 21 after induction of OA. The degree of hyper nociception (pain) was evaluated daily by measuring the mechanical threshold required to induce joint flexion and foot withdrawal reflex. After 56 days, the groups of animals were analyzed using the OARSI scoring system. An increased antinociceptive effect was observed with 30 g and 100 g doses of galactomannan from day 15 to the endpoint at day 56. Joint damage was also reduced in OA-affected animals following the administration of 100 g galactomannan, compared with the saline placebo group (5.9 ± 1.8 vs. 19.0 ± 1.8, respectively; $P < 0.05$) [105].

4.2. Fatty acids

Fatty acids are one of the constituents of lipids and are in the structural form of carboxylic acids with saturated or unsaturated aliphatic chains [106]. Some fatty acids in Arecaceae are lauric acid, myristic acid, oleic acid, linoleic acid, and linolenic acid [100, 107]. The two last compounds, (a) linoleic acid and (b) linolenic acid have the structure as shown in Figure 8.

Besides medicine and physical treatment, nutraceuticals, such as omega-3 and omega-6 fatty acids, can improve symptoms, prevent cartilage, or slow the degenerative process [108]. A study determined the effect of fish oil omega-3 fatty acid supplementation on the dose of carprofen in dogs with OA. The study design involved a randomized, controlled, and multisite clinical trial. 131 dogs with stable chronic OA were examined at 33 private veterinary hospitals in the United States. The dose of carprofen over three weeks was approximately 4.4 mg/kg/day in all dogs. Dogs were then randomly assigned to a diet supplemented with omega-3 fatty acid fish oil or a control diet low in

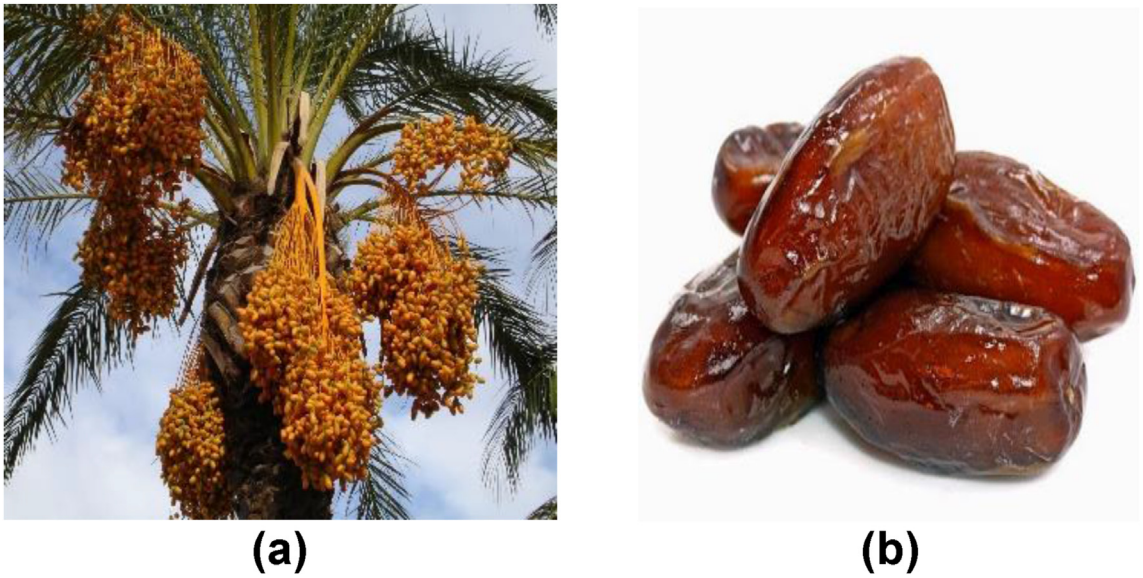


Figure 4. (a) Date palm tree; date palm fruits [92].

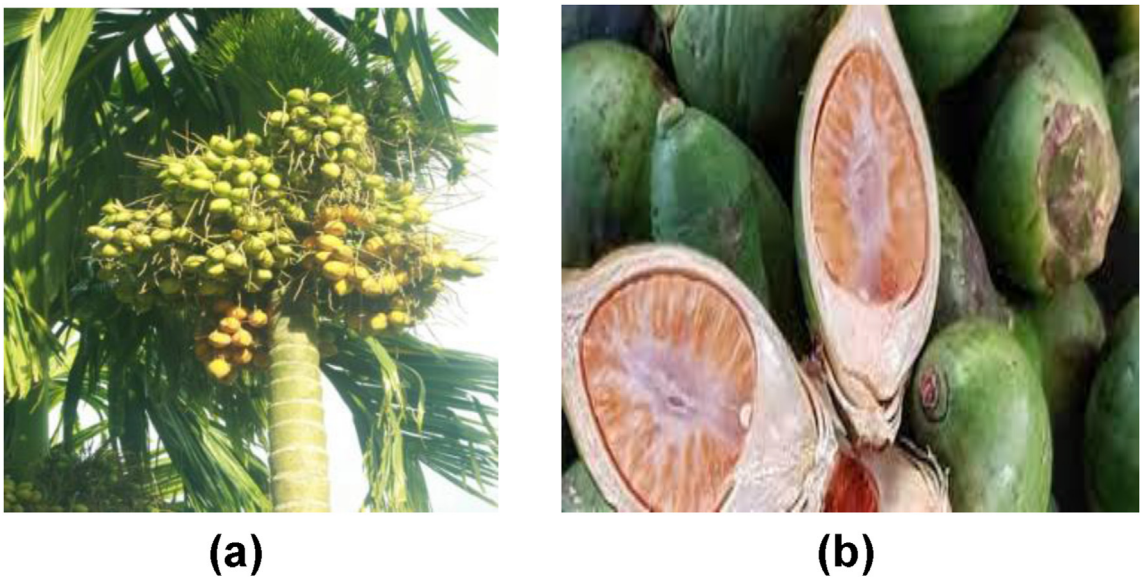


Figure 5. (a) Betel nut tree; (b) betel nut fruits [100].

omega-3 fatty acids. The investigators decided about increasing or decreasing the carprofen dose after 3, 6, 9, and 12 weeks, based on the investigator's assessment of 5 clinical signs and the owner's rating of 15 signs. The results of linear regression analysis showed that the dose of carprofen decreased significantly more rapidly over the 12-week study period in the dog fed the supplement diet than in the control group. The distribution of the change of carprofen dose in the control group was significantly different from the distribution of the change of dose for the dogs in the test group, with the conclusion that dogs with chronic OA who received carprofen showed a clinically relevant reduction in the dose of carprofen by a diet supplemented with omega-3 fatty acid fish oil [109].

4.3. Flavonoids

Research has also been carried out on the role of flavonoids as anti-inflammatory and chondroprotective agents. For example, quercetin, with the structure shown in Figure 3, has a therapeutic effect in OA mice, which is related to the inhibition of IL-1β and tumor necrosis factor (TNF) production via the Toll-like receptor (TLR)-4/NF-kB pathway. The method used was a mouse model of OA, following intra-articular injection with papain. Changes in knee diameter, toe volume, and histopathology were measured, and ELISA assessed IL-β and TNF levels. The relative expression of TLR-4 and NF-kB was evaluated by western blotting, proving that the administration of quercetin reduced the changes in knee diameter and toe volume in OA rats, as well as the serum levels of IL-1β and TNF. Expression of TLR-4 and NF-kB was also significantly suppressed [110].

In vitro, quercetin suppressed the expression of matrix-degrading proteases and inflammatory mediators and promoted the production of cartilage anabolic factors in the chondrocytes of IL-1β-induced rats. Quercetin also exhibited anti-apoptotic effects by decreasing reactive oxygen species (ROS), restoring mitochondrial membrane potential (MMP), and inhibiting the Caspase-3 pathway in the chondrocytes of apoptotic rats. In addition, quercetin induced M2 macrophage polarization and upregulated the expression of transforming growth factor (TGF-β) and insulin-like growth factor (IGF), which in turn created a pro-

Figure 6. (a) Sago tree; (b) sago fruits [103].

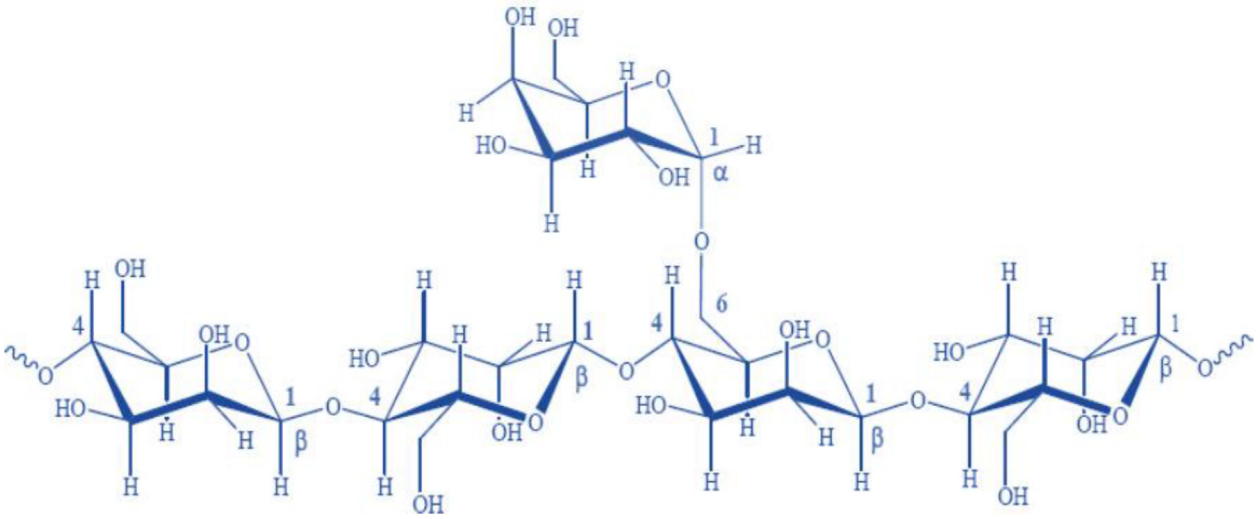


Figure 7. Structure of galactomannan.

chondrogenic microenvironment for chondrocytes and promoted GAG synthesis in chondrocytes [111].

In vivo, intra-articular injection of quercetin reduced cartilage degradation and chondrocyte apoptosis in the mouse model of OA. In addition, the expression of TGF-β1 and TGF-β2 in synovial fluid and the ratio of M2 macrophages in the synovial membrane increased. This study proved that quercetin exerts anti-OA effects by inhibiting inflammation and apoptosis of chondrocytes, modulating the polarization of synovial macrophages to M2 macrophages, and creating a pro-chondrogenic environment for chondrocytes to promote cartilage repair under an OA environment [112]. Another study suggested that quercetin can up-regulate SOD and TIMP-1, down-regulate MMP-13, and promote OA degeneration by attenuating the oxidative stress response and inhibiting cartilage extracellular matrix degradation [113].

Other flavonoid compounds, such as luteolin, exert cytoprotective effects against oxidative injury, inflammatory response, and extracellular matrix (ECM) degradation in primary murine chondrocytes through activation of the AMPK/Nrf2 and AMPK signaling pathways [114]. In addition, luteolin also protects mouse chondrocytes stimulated by IL-1β and monosodium iodoacetate (MIA)-induced OA models [115]. At the same time, isorhamnetin has an anti-inflammatory effect by reducing knee swelling caused by MIA, significantly reducing articular cartilage damage in mice. Isorhamnetin inhibits NO and PGE2 production, iNOS and COX-2 expression, and COMP, CTX-II, and osteopontin production [116]. The structures of the three flavonoids, (a) quercetin; (b) luteolin; (c) isorhamnetin are shown in Figure 9.

4.4. Phenolics and polyphenols

Phenolic compounds such as ferulic acid and coumaric acid prevent IL-1β-induced OA and have anti-OA potential [117, 118]. Polyphenols such as epicatechin increase the articular cartilage structure and chondrocyte cellularity and reduce joint cartilage degradation by suppressing nitric oxide production and tissue catabolism by proteases, suppressing inflammation [119]. The structure of (a) ferulic acid; (b) coumaric acid; and (c) epicatechin are shown in Figure 10.

4.5. Alkaloids

Arecoline, with the structure depicted in Figure 11, is the primary type of alkaloid in the *Areca* nut (*A. catechu*). It has an anti-inflammatory effect that can support the management of OA [120]. The effects of that compound on bone have been investigated using an *in vivo* LPS-induced mouse model. The results showed that arecoline prevents bone loss by suppressing osteoclast genesis and promoting osteoblast genesis [121]. However, more research needs to be done regarding its benefits on cartilage to see the potential for treating OA.

4.6. Steroids

One steroid compound, stigmasterol, has an anti-OA effect. Newborn rat chondrocytes and human OA chondrocytes were used in primary culture stimulated with or without IL-1β (10 ng/mL) for 18 h. Next, the cells were incubated for 48 h with stigmasterol (20 mg/mL), then compared with untreated cells. The results suggested that stigmasterol inhibited several pro-inflammatory mediators and matrix degradation commonly involved in OA-induced cartilage degradation via inhibiting the NF-kB pathway [122]. Other steroid compounds, namely campesterol and spirostane, were reported to have anti-inflammatory effects [123, 124]. The structure of the three steroids, (a) stigmasterol; (b) campesterol; (c) spirostane are shown in Figure 12.

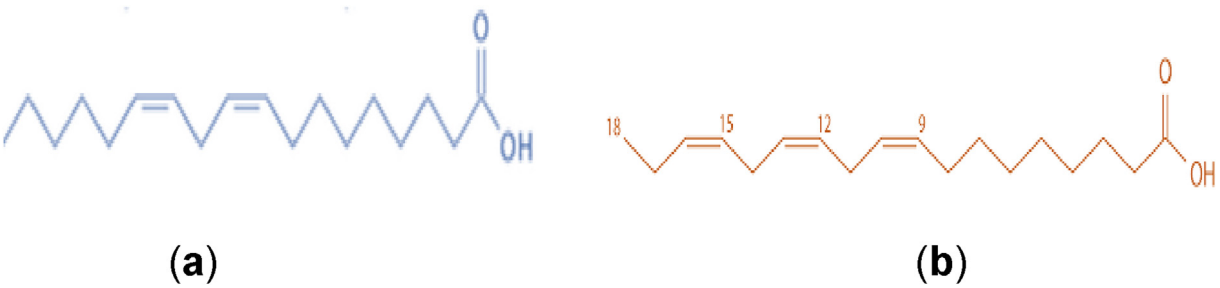


Figure 8. Structure of fatty acids: **(a)** linoleic acid; **(b)** linolenic acid.

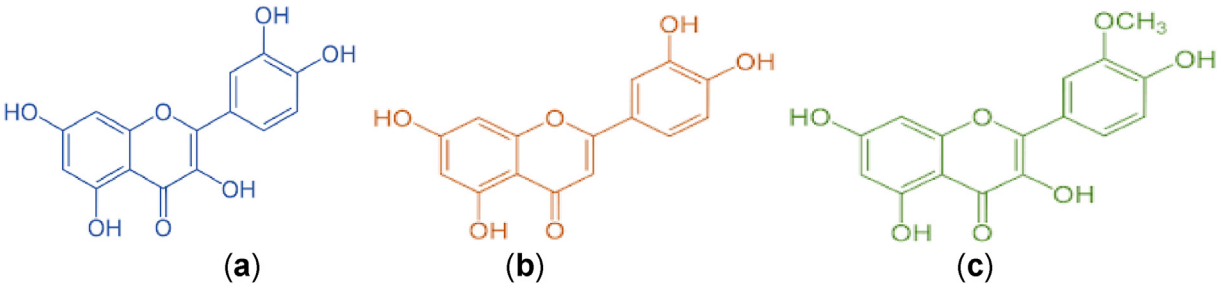


Figure 9. Structure of flavonoids: (**a**) quercetin; (**b**) luteolin; (**c**) isorhamnetin.

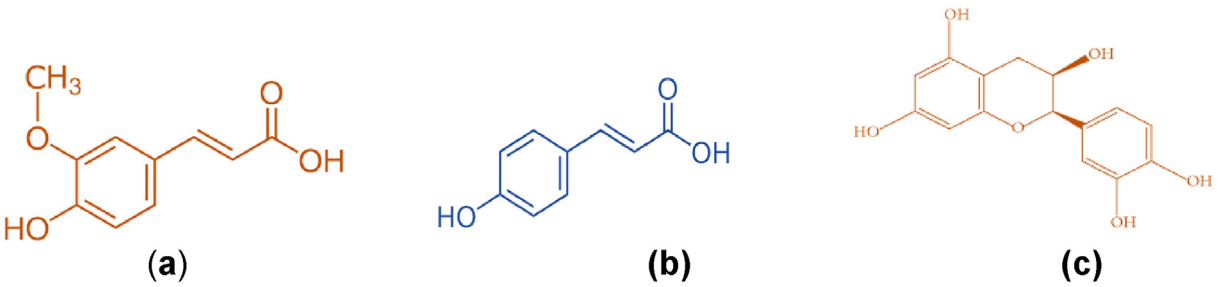


Figure 10. Structure of phenolics and polyphenol: (**a**) ferulic acid; (**b**) coumaric acid; (**c**) epicatechin.

Some compounds in the Arecaceae family that have anti-osteoarthritis activities are shown in Table 1.

5. Development of anti-inflammation with a structure-activity approach

The development of drugs is commonly carried out using a structure-activity relationship approach, including the search for anti-inflammatory medications [125]. Studying the structural relationship between the activity of a drug is very useful in designing new drugs with more significant action, selectivity, lower toxicity, and fewer side effects. Any active compound that undergoes structural changes can alter its biological activity [126].

5.1. Polysaccharides

The anti-inflammatory activity of polysaccharides is closely related to their chemical structure, especially their monosaccharide composition, conformation, glycosidic bond position, and molecular mass [127, 128]. Research revealed that the monosaccharide composition significantly affects polysaccharide bioactivity, including anti-inflammatory effects. For example, glucans, homopolymers of D-glucose, were proven to have therapeutic effects on inflammatory diseases [129]. In addition, the conformation of the polysaccharide chain tends to change with variations in molecular weight, which is associated with anti-inflammatory effect change [130], as well as the type and position of the glycosidic bond.

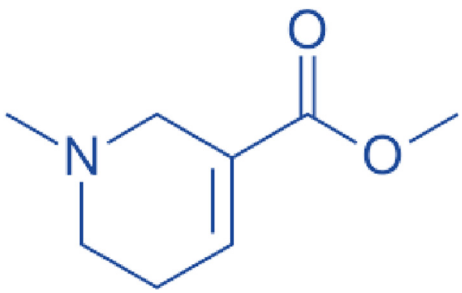


Figure 11. Structure of arecoline.

Studies have shown that the (1→3) binding of -D-glucose satisfies the requirements of the anti-inflammatory pharmacophore of *Cipangopaludina chinensis* (CCPSn) [131].

Furthermore, the molecular mass of polysaccharides and the presence of sulfate also affect biological activity. In a study on the anti-inflammatory activity of polysaccharides from brown algae *Sargassum cristaefolium*, a polysaccharide with a molecular mass of 386.1 kDa and a sulfate content of 9.42% showed higher NO inhibitory activity in LPS-stimulated RAW264.7. It is suspected that the sulfate content of the polysaccharide may affect its binding to cell receptors, thereby affecting NO production in cells [132].

One of the polysaccharides found in the Arecaceae family is galactomannan. Research suggests galactomannan from *Delonix regia* has anti-inflammatory and antinociceptive effects [133]. Galactomannan also reduces inflammatory symptoms by decreasing neutrophil infiltration, leukocyte migration and adhesion, TNFα production, and thiobarbituric acid reactive species (TBARS) [134].

The effect of changes in the chemical structure and bioactivity of galactomannans has been widely reported. Most modified galactomannans provide enhanced pharmacological effects; however, several studies revealed the bioactivity reduction after chemical changes to the original structure [135].

5.2. Flavonoids

Flavonoids are secondary metabolites with anti-inflammatory activity [136]. This group has a variety of structures that allow it to interact with different targets. The basic structure of flavonoids is shown in Figure 13.

Research shows that flavonoids' hydroxyl group (−OH) significantly affects anti-inflammatory activity. An OH group at positions C-5 and C-4′ will increase the effect, while an OH group at positions C-6, C-7, C-8, and C-3′ will weaken it. Most of the anti-inflammatory activities of flavonoids are via the NF-kB, MAPK, and JNK-STAT pathways, with the possible cell-binding targets, are kinases, aryl hydrocarbon receptors (AhR), G-protein-coupled receptors, and estrogen receptors [137].

Flavonols, such as isorhamnetin, kaempferol, and quercetin, inhibit NO production, iNOS protein and mRNA expression, and NF-kB activation. Quercetin and kaempferol also influence STAT-1. Thus, quercetin inhibits LPS-induced STAT-1 and has an inhibitory effect on iNOS

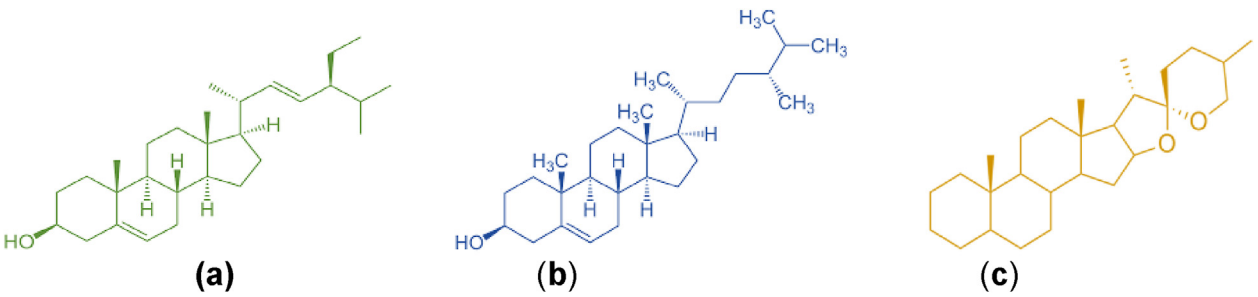
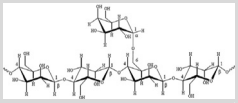
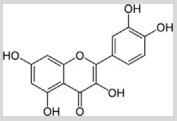
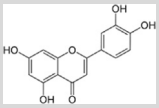
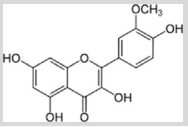
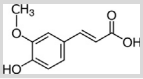
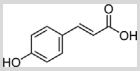
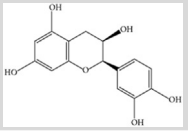
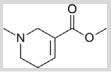
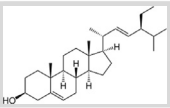
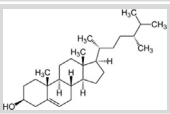
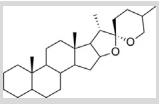


Figure 12. Several types of steroids in Arecaceae: (**a**) stigmasterol; (**b**) campesterol; (**c**) spirostane.

Table 1. Some compounds in the Arecaceae family that have anti-OA activities.

No.	Sources/Species of Arecaceae	Metabolites/ Compounds	Structure	Anti-osteoarthritis Activities	Ref.
1	*Arenga pinnata*, *Borassus flabellifer*, *Nypa fruticans*	Polysaccharide/ galactomannan		Reduces the level of joint damage and pain in rats with induced osteoarthritis and has anti-inflammatory activity	[105]
2	*Borassus flabellifer*, *Nypa fruticans*	Fatty Acid/linolenic acid (omega 3)		Improves symptoms and prevents the degenerative process in cartilage	[108, 109]
		Linoleic acid (omega 6)			
3	*Phoenix dactylifera*, *Areca catechu*	Flavonoid/quercetin		Inhibits the production of interleukin (IL)-1β and TNF via the TLR-4/NF-kB pathway, suppresses the expression of matrix-degrading proteases and inflammatory mediators, promotes the production of cartilage anabolic factors in IL-1β-induced mouse chondrocytes, upregulates SOD and TIMP-1, downregulates MMP-13, and promotes osteoarthritis degeneration by attenuating the oxidative stress response and inhibiting cartilage extracellular matrix degradation.	[112, 113]
	Phoenix dactylifera, *Areca catechu*	Luteolin		Cytoprotective against oxidative injury, inflammatory response, and ECM degradation in primary murine chondrocytes through activation of the AMPK/Nrf2 and AMPK signaling pathways, protects rat chondrocytes stimulated by IL-1β and monosodium iodoacetate (MIA)-induced osteoarthritis model.	[114, 115]
	Phoenix dactylifera, *Areca catechu*	Isorhamnetin		The anti-inflammatory effect reduces knee swelling caused by MIA, significantly reducing articular cartilage damage in mice. Isorhamnetin inhibits NO and PGE2 production, iNOS and COX-,2 expression, and COMP, CTX-II, and osteopontin (OPN) production.	[116]
4	*Phoenix dactylifera*, *Areca catechu*	Phenolic and Polyphenol/Ferulic acid		It prevents IL-1β-induced osteoarthritis, indicating that ferulic acid has the potential for osteoarthritis.	[117]
	Phoenix dactylifera, *Areca catechu*	Coumaric acid		Attenuates IL-1β-induced inflammatory response and cellular senescence through inhibition of MAPK and NF-kB signaling pathways in chondrocytes	[118]
	Phoenix dactylifera, *Areca catechu*	Epicatechin		Increases articular cartilage structure and chondrocyte cellularity and reduces joint cartilage degradation by suppressing nitric oxide production, tissue catabolism by proteases, and suppressing inflammation	[119]
5	*Areca catechu*	Alkaloid/arecolin		Anti-inflammatory activity	[120]
6	*Phoenix dactylifera*, *Areca catechu*	Steroid/stigmasterol		Inhibits several pro-inflammatory mediators and matrix degradation commonly involved in osteoarthritis-induced cartilage degradation via inhibition of the NF-kB pathway	[121]
	Phoenix dactylifera, *Areca catechu*	Campesterol		Anti-inflammatory activity	[123]
	- *Borassus flabellifer*	- Spirostane		Anti-inflammatory activity	[124]

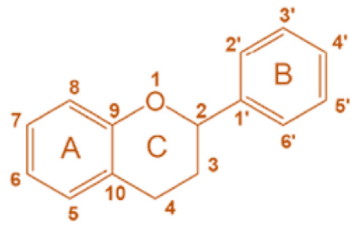


Figure 13. The basic structure of flavonoids.

expression and NF-kB activation. Flavonoids and their derivatives (glycosides, rhamnosides, rutinosides, or neohesperidosides) have several structural requirements for inhibiting NO production, namely the C-2,3 double bond and OH groups at C-7 and C-4' [138].

Other studies have shown the effect of flavonoids on lipoxygenase and peroxidase inhibition. The most potent lipoxygenase inhibitor was kaempferol with one –OH group located at position 4′ in ring B, which had an activity of 21.2 ± 2.03 per mole of compound. The weakest inhibition was observed for diosmetin with a hydroxyl group at the 3′ position and a methoxy group at 4′ in ring B, which had an activity of 1.17 ± 0.77 per mole. Peroxidase was most strongly inhibited by quercetin (22.7 ± 0.05) with two hydroxyl groups on ring B at 3′ and 4. The weakest peroxidase inhibitor was genkwanin (0 ± 0.16), with one hydroxyl group at position 4′ on ring B and a methoxy group at position 7 on ring A. The results showed that weak peroxidase inhibition was related to the reducing properties of phenol, and lipoxygenase inhibition was associated with the antioxidant properties of flavonoids [139].

Luteolin and its glycoside derivates, such as cynaroside, cesioside, isoorientin, and stereolensin, were tested in vitro to determine their ability to inhibit enzymes for synthesizing thromboxane B2 and leukotrienes B4 and their hydrogen peroxide radical scavenging activity. Luteolin exhibited high inhibitory activity regarding the synthesis of thromboxane and leukotrienes; cynaroside and cesioside had moderate inhibitory activity against both enzyme synthesis pathways. At the same time, isoorientin and stereolensine showed good selective activity against thromboxane synthesis. Luteolin and its glycoside derivatives showed good antidote activity for hydrogen peroxide. The results showed that the activity of luteolin and its glycosides reduces the synthesis of arachidonic acid and hydrogen peroxide radicals, depending on their molecular structure. The presence of an ortho-dihydroxy group in ring B and the pattern of OH substitution at the C-5 position of ring A significantly influence the anti-inflammatory activity of flavonoids [140].

6. Potential development of arecaceae as natural anti-OA agents

The need for anti-OA drugs will increase in the future. Based on the available research data, at least 26,000 individuals per 1 million population aged 45 years are expected to experience OA in 2032 compared to 2012. These findings indicate that efforts are needed to develop new effective treatments for OA [141]. The current treatment of OA generally uses anti-inflammatory drugs such as NSAIDs, which have serious side effects [142]. Treatments sourced from natural ingredients may be an option in treating diseases, including OA.

Based on the articles that have been collected, the plant family Arecaceae sp. can potentially be developed as a natural anti-OA agent. This plant family contains both primary and secondary metabolites that have anti-inflammatory and chondroprotective effects, so they are helpful in the treatment of OA. For example, galactomannan polysaccharide compounds found in sugar palm, palmyra palm, and nipa palm fruits can be developed in OA treatments. Galactomannan has anti-inflammatory and chondroprotective effects that can reduce cartilage degradation [105, 143]. According to the research, protein-free galactomannan provides a better anti-OA result.

In contrast, structural modification of galactomannan in both the oxide and sulfate forms did not have a significant effect [144]. Therefore, galactomannan in Arecaceae sp. can be developed as an anti-OA nutraceutical. In addition, several other compound groups, such as flavonoids in dates palm and betel nut, have anti-osteoarthritis effects as chondroprotective and anti-inflammatory. Hereafter, they promise to be developed as natural anti-osteoarthritis [106].

7. Conclusions

OA is a chronic inflammation of the joints caused by reduced joint fluid and cartilage matrix components, resulting in cartilage damage, pain, deformity, and limitation of movement. Its prevalence is increasing yearly and involves various treatments and medications. OA treatment includes maintaining an ideal BMI, physiotherapy, rest, and warm compresses. Meanwhile, the medicine used involves anti-inflammatory drugs and chondroprotective agents. Currently, NSAID drugs are commonly used to treat OA, but those medicines have many side effects. Therefore, natural pharmaceuticals and nutraceuticals may be explored as alternative options. Arecaceae plants include sugar palm (*A. pinnata*), nipa palm (*N. fruticans*), palmyra palm (*B. flabellifer*), date palm (*P. dactylifera*), and betel nut (*A. catechu*), have potential anti-OA action. This potency cannot be separated from the role of primary and secondary metabolites that have anti-inflammatory and chondroprotective effects, such as polysaccharides (galactomannan), fatty acids (linoleic and linolenic acids), flavonoids (quercetin, kaempferol, luteolin), phenolics (coumaric acid, ferulic acid), polyphenols (epicatechin), and steroids (stigmasterol, campesterol, spirostane). This plant family can be utilized as the safe and economical natural anti-OA because it has been consumed as daily food and is very easy to find. Hence, this family plant is prospective to be developed either as a preparation or for fresh food directly consumed.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Funding statement

This work was supported by the Education Financing Service Center Ministry of Education, Culture, Research, and Technology and the Educational Fund Management Institution Ministry of Finance of the Republic of Indonesia, registration number 202101121602; and the Research and Public Service of Bandung Institute of Technology, Indonesia, number LPPM.PM-8-57-2022.

Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

References

[1] S. Zhu, J. Zhu, G. Zhen, Y. Hu, S. An, Y. Li, X. Cao, Subchondral bone osteoclasts induce sensory innervation and osteoarthritis pain, J. Clin. Investig. 129 (3) (2019) 1076–1093.
[2] B. Xia, D. Chen, J. Zhang, S. Hu, H. Jin, P. Tong, Osteoarthritis pathogenesis: a review of molecular mechanisms, Calcif. Tissue Int. 95 (6) (2014) 495–505.
[3] A. Mobasheri, M. Batt, An update on the pathophysiology of osteoarthritis, Ann. Phys. Rehabil. Med. 59 (5-6) (2016) 333–339.

[4] J.E. Chrubasik, B.D. Roufogalis, S. Chrubasik, Evidence of effectiveness of herbal antiinflammatory drugs in the treatment of painful osteoarthritis and chronic low back pain, Phytother Res. 21 (7) (2007) 675–683.

[5] B.N. Lindler, K.E. Long, N.A. Taylor, W. Lei, Use of herbal medications for treatment of osteoarthritis and rheumatoid arthritis, Medicine (Baltim.) 7 (11) (2020) 67.

[6] R. Choopani, A. Ghourchian, H. Hajimehdipoor, M. Kamalinejad, Scientific evaluation of pharmacological treatment of osteoarthritis in the Canon of medicine, J. Evid. based Complementary Altern. Med. 21 (3) (2016) 228–234.

[7] C. Cooper, R. Chapurlat, N. Al-Daghri, G. Herrero-Beaumont, O. Bruyère, F. Rannou, R. Roth, D. Uebelhart, J.Y. Reginster, Safety of oral non-selective non-steroidal anti-inflammatory drugs in osteoarthritis: what does the literature say? Drugs Aging 36 (1) (2019) 15–24.

[8] N. Isailovic, K. Daigo, A. Mantovani, C. Selmi, Interleukin-17 and innate immunity in infections and chronic inflammation, J. Autoimmun. 60 (2015) 1–11 [.

[9] G. Pedraza-Alva, L. Pérez-Martínez, L. Valdez-Hernández, K.F. Meza-Sosa, M. Ando-Kuri, Negative regulation of the inflammasome: keeping inflammation under control, Immunol. Rev. 265 (1) (2015) 231–257.

[10] L. Laadhar, M. Zitouni, M. Kalle-Sellami, M. Mahjoub, S. Sellami, S. Makni, Physiopathology of osteoarthritis. From normal cartilage to osteoarthritic cartilage: risk factors and inflammatory mechanisms, Rev. Med. Interne 28 (8) (2017) 531–536.

[11] N. Ishiguro, T. Kojima, A.R. Poole, Mechanism of cartilage destruction in osteoarthritis, Nagoya J. Med. Sci. 65 (3-4) (2002) 73–84 [PMID: 12580533].

[12] K.D. Rainsford, Anti-inflammatory drugs in the 21st century, in: Inflammation in the Pathogenesis of Chronic Diseases, Biomedical Research Centre Sheffield Hallam University: Howard Street, Sheffield, SI 1WB, UK, 2007, pp. 3–27.

[13] B.J. Whittle, Gastrointestinal effects of nonsteroidal anti-inflammatory drugs, Fundam. Clin. Pharmacol. 17 (3) (2003) 301–313.

[14] J.H. Rubenstein, L. Laine, The hepatotoxicity of non-steroidal anti-inflammatory drugs, Aliment. Pharmacol. Ther. 20 (4) (2004) 373–380.

[15] S. Guzmán, A. Gato, M. Lamela, M. Freire-Garabal, J.M. Calleja, Anti-inflammatory and immunomodulatory activities of polysaccharide from *Chlorella stigmatophora* and *Phaeodactylum tricornutum*, Phytother Res. 17 (6) (2003) 665–670.

[16] S.A. Hussain, N.A. Jassim, I.T. Numan, I.I. Al-Khalifa, T.A. Abdullah, Anti-inflammatory activity of silymarin in patients with knee osteoarthritis, Saudi Med. J. 30 (1) (2009) 98–103.

[17] S. Li, X. Liu, X. Chen, L. Bi, Research progress on anti-inflammatory effects and mechanisms of alkaloids from Chinese medical herbs, J. Evid. Based Complementary Altern. Med. 2020 (2020) 1–10.

[18] T. Kim, B. Song, K.S. Cho, I.S. Lee, Therapeutic potential of volatile terpenes and terpenoids from forests for inflammatory diseases, Int. J. Mol. Sci. 21 (6) (2020) 2187.

[19] S.S. Patel, J.K. Savjani, Systematic review of plant steroids as potential anti-inflammatory agents: current status and future perspectives, J. Phytopharmacol. 4 (2) (2015) 121–125.

[20] S. Sukhikh, O. Babich, A. Prosekov, N. Patyukov, S. Ivanova, Future of chondroprotectors in the treatment of degenerative processes of connective tissue, Pharmaceuticals 13 (9) (2020) 220.

[21] C. Bottegoni, R.A. Muzzarelli, F. Giovannini, A. Busilacchi, A. Gigante, Oral chondroprotection with nutraceuticals made of chondroitin sulphate plus glucosamine sulphate in osteoarthritis, Carbohydr. Polym. 109 (2014) 126–138.

[22] M. Guerrini, D. Beccati, Z. Shriver, A. Naggi, K. Viswanathan, A. Bisio, I. Capila, J.C. Lansing, S. Guglieri, B. Fraser, A. Al Hakim, N.S. Gunay, Z. Zhang, L. Robinson, L. Buhse, M. Nasr, J. Woodcock, R. Langer, G. Venkataraman, R.J. Linhardt, B. Casu, G. Torri, R. Sasisekharan, Oversulfated chondroitin sulfate is a contaminant in heparin associated with adverse clinical events, Nat. Biotechnol. 26 (6) (2008) 669–675.

[23] Q. Chen, X. Shao, P. Ling, F. Liu, G. Han, F. Wang, Recent advances in polysaccharides for osteoarthritis therapy, Eur. J. Med. Chem. 139 (2017) 926–935.

[24] S. Bowman, M.E. Awad, M.W. Hamrick, M. Hunter, S. Fulzele, Recent advances in hyaluronic acid based therapy for osteoarthritis, Clin. Transl. Med. 7 (1) (2018) 1–11.

[25] N.S. Shuborna, T. Chaiyasamut, W. Sakdajeyont, C. Vorakulpipat, M. Rojvanakarn, N. Wongsirichat, Generation of novel hyaluronic acid biomaterials for study of pain in third molar intervention: a review, J. Dent. Anesth. Pain Med. 19 (1) (2019) 11–19.

[26] Y.W. Lin, C.H. Fang, F.Q. Meng, C.J. Ke, F.H. Lin, Hyaluronic acid loaded with cerium oxide nanoparticles as antioxidant in hydrogen peroxide induced chondrocytes injury: an in vitro osteoarthritis model, Molecules 25 (19) (2020) 4407.

[27] A. Van de Vyver, S. Clockaerts, C.H. van de Lest, W. Wei, J. Verhaar, G.J. Van Osch, Y.M. Bastiaansen-Jenniskens, Synovial fluid fatty acid profiles differ between osteoarthritis and healthy patients, Cartilage 11 (4) (2020) 473–478.

[28] K. Zhao, Y. Wen, V. Bunpetch, J. Lin, Y. Hu, X. Zhang, Y. Xie, S. Zhang, O. Hongwei, Hype or hope of hyaluronic acid for osteoarthritis: integrated clinical evidence synthesis with multi-organ transcriptomics, J. Ortho. Transl. 32 (2022) 91–100.

[29] J.A. Roman-Blas, S. Castañeda, O. Sánchez-Pernaute, R. Largo, G. Herrero-Beaumont, CS/GS Combined Therapy Study Group; Rosas Gómez de Salazar, J. C. (Combined treatment with chondroitin sulfate and glucosamine sulfate shows no superiority over placebo for reduction of joint pain and functional impairment in patients with knee osteoarthritis: a six-month multicenter, randomized, double-blind, placebo-controlled clinical trial, Arthritis Rheumatol. 69 (1) (2017) 77–78.

[30] W.J. Baker, T.L. Couvreur, Biogeography and distribution patterns of Southeast Asian palms, in: Biotic Evolution and Environmental Change in Southeast Asia, Cambridge University Press, Cambridge, 2012, pp. 164–188.

[31] E. Sovia, D. Anggraeny, Sugar palm fruits (*Arenga pinnata*) as potential analgesics and anti-inflammatory agent, Molecular and Cellular Biomedical Sciences 3 (2) (2019) 107–114.

[32] N.L. Rahmah, N. Hidayat, B.K. Hajar, Glucosamine production from palmyrah (*Borassus flabellifer* L.) seeds (a study of precursor type and concentration), in: IOP Conference Series: Earth and Environmental Science, Universitas Brawijaya, Indonesia, 2018, pp. 18–20.

[33] H. Khotimah, W. Riawan, H.A. Trisnaini, E. Zubaidah, Sugar palm fruit (*Arenga pinnata*) diminish pain and inflammatory symptoms of osteoarthritis in male Wistar rat (Rattus norvegicus), Res. J. Pharm. Technol. 11 (9) (2018) 3745–3751.

[34] N.L. Rahmah, I.A. Dewi, B.S.D. Dewanti, C.G. Perdani, D.T. Prayudi, A. Ihwah, W.G. Rohmah, Reaction optimization study on extraction of crude glucosamine siwalan fruit seeds (*Borassus flabellifer* L.), J. Teknol. Pertan. 17 (1) (2016) 1–12.

[35] C.B. Carballo, Y. Nakagawa, I. Sekiya, S.A. Rodeo, Basic science of articular cartilage, Clin. Sports Med. 36 (3) (2017) 413–425.

[36] K.D. Brandt, P. Dieppe, E.L. Radin, Etiopathogenesis of osteoarthritis, Rheum. Dis. Clin. N. Am. 34 (3) (2008) 531–559.

[37] C. Chung, J.A. Burdick, Engineering cartilage tissue, Adv. Drug Deliv. Rev. 60 (2) (2008) 243–262.

[38] G.S. Man, G. Mologhianu, Osteoarthritis pathogenesis–a complex process that involves the entire joint, J. med. life 7 (1) (2014) 37.

[39] L. Zheng, Z. Zhang, P. Sheng, A. Mobasheri, The role of metabolism in chondrocyte dysfunction and the progression of osteoarthritis, Ageing Res. Rev. 66 (2021), 101249.

[40] S.H.J. Wong, K.Y. Chiu, C.H. Yan, Osteophytes, J. Orthop. Surg. 24 (3) (2016) 403–410.

[41] H.T. Liang, X.C. Feng, T.H. Ma, Water channel activity of plasma membrane affects chondrocyte migration and adhesion, Clin. Exp. Pharmacol. Physiol. 35 (1) (2007) 7–10.

[42] M. Cross, E. Smith, D. Hoy, S. Nolte, I. Ackerman, M. Fransen, L. March, The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study, Ann. Rheum. Dis. 73 (7) (2014) 1323–1330.

[43] R.I. Kementrian Kesehatan, Laporan Nasional Riskesdas 2018, Badan Penerbit Badan Penelitian dan Pengembangan Kesehatan, Jakarta, Indonesia, 2019, pp. 175–178.

[44] G. Musumeci, F.C. Aiello, M.A. Szychlinska, M. Di Rosa, P. Castrogiovanni, A. Mobasheri, Osteoarthritis in the XXIst century: risk factors and behaviours that influence disease onset and progression, Int. J. Mol. Sci. 16 (3) (2015) 6093–6112.

[45] X. Wang, W.M. Oo, J.M. Linklater, What is the role of imaging in the clinical diagnosis of osteoarthritis and disease management? Rheumatology 57 (suppl_4) (2018) iv51–iv60.

[46] S. Sutton, A. Clutterbuck, P. Harris, T. Gent, S. Freeman, N. Foster, A. Mobasheri, The contribution of the synovium, synovial derived inflammatory cytokines and neuropeptides to the pathogenesis of osteoarthritis, Vet. J. 179 (1) (2009) 10–24.

[47] K. Lu, F. Ma, D. Yi, H. Yu, L. Tong, D. Chen, Molecular signaling in temporomandibular joint osteoarthritis, J. Ortho. Transl. 32 (2022) 21–27.

[48] M. Rahman, A. Sahoo, S. Beg, Herbal anti-arthritic drug discovery tool based on inflammatory biomarkers, in: *Biomarkers as Targeted Herbal Drug* Discovery, Apple Academic Press, New Jersey, US, 2021, pp. 27–41.

[49] Z. Zhuang, G. Ye, B. Huang, Kaempferol alleviates the interleukin-1β-induced inflammation in rat osteoarthritis chondrocytes via suppression of NF-κB, Med.Sci. Monit. 23 (2017) 3925.

[50] M.H. Nasrabadi, M. Parsivand, N. Mohammadi, N.A. Moghaddam, Comparison of Elaeagnus angustifolia L. extract and quercetin on mouse model of knee osteoarthritis, J. Ayurveda Integr. Med. 13 (2) (2022), 100529.

[51] O. Gabay, C. Sanchez, C. Salvat, F. Chevy, M. Breton, G. Nourissat, F. Berenbaum, Stigmasterol: a phytosterol with potential anti-osteoarthritic properties, Osteoarthritis Cartilage 18 (1) (2010) 106–116.

[52] M. Abshirini, B.L. Ilesanmi-Oyelere, M.C. Kruger, Potential modulatory mechanisms of action by long-chain polyunsaturated fatty acids on bone cell and chondrocyte metabolism, Prog. Lipid Res. 83 (2021), 101113.

[53] H.K. Vincent, K. Heywood, J. Connelly, R.W. Hurley, Obesity and weight loss in the treatment and prevention of osteoarthritis, PM&R 4 (5) (2012) S59–S67.

[54] A. Denny, Intervensi fisioterapi pada kasus osteoarthritis genu di RSPAD Gatot Soebroto, J. Sos. Hum. Terap. 1 (2) (2019).

[55] M. Hannan, E. Suprayitno, H. Yuliyana, Pengaruh terapi kompres hangat terhadap penurunan nyeri sendi osteoarthritis pada lansia di Posyandu Lansia Puskesmas Pandian Sumenep, Wiraraja Medika 9 (1) (2019) 1–10.

[56] E.R. Sherwood, T. Toliver-Kinsky, Mechanisms of the inflammatory response, Best Pract. Res. Clin. Anaesthesiol. 18 (3) (2004) 385–405.

[57] R. Maia-Marques, I.M. Nascimento, P.S. Lauria, E.C. da Silva, D.F. Silva, L.L. Casais-e-Silva, Inflammatory mediators in the pronociceptive effects induced by *Bothrops leucurus* snake venom: the role of biogenic amines, nitric oxide, and eicosanoids, Toxicology 448 (2021), 152649.

[58] W.D.M. Cruvinel, D. Mesquita Júnior, J.A.P. Araújo, T.T.T. Catelan, A.W.S.D. Souza, N.P.D. Silva, L.E.C. Andrade, Immune system: Part I. Fundamentals of innate immunity with emphasis on molecular and cellular mechanisms of inflammatory response, Rev. Bras. Reumatol. 50 (2010) 434–447.

[59] C.R. Morris, I.M. Harvey, W.S.L. Stebbings, C.T.M. Speakman, H.J. Kennedy, A.R. Hart, Anti-inflammatory drugs, analgesics and the risk of perforated colonic diverticular disease, J. Br. Surg. 90 (10) (2003) 1267–1272.

[60] G. Ruoff, M. Lema, Strategies in pain management: new and potential indications for COX-2 specific inhibitors, J. Pain Symptom Manag. 25 (2) (2003) 21–31.

[61] M.C. Terencio, M.L. Ferrándiz, M.C. Carceller, R. Ruhí, P. Dalmau, J. Vergés, M.J. Alcaraz, Chondroprotective effects of the combination chondroitin sulfate-glucosamine in a model of osteoarthritis induced by anterior cruciate ligament transection in ovariectomised rats, Biomed. Pharmacother. 79 (2016) 120–128.

[62] C. Bottegoni, R.A. Muzzarelli, F. Giovannini, A. Busilacchi, A. Gigante, Oral chondroprotection with nutraceuticals made of chondroitin sulphate plus glucosamine sulphate in osteoarthritis, Carbohydr. Polym. 109 (2014) 126–138.

[63] B. Gallagher, F.P. Tjoumakaris, M.I. Harwood, R.P. Good, M.G. Ciccotti, K.B. Freedman, Chondroprotection and the prevention of osteoarthritis progression of the knee: a systematic review of treatment agents, Am. J. Sports Med. 43 (3) (2015) 734–744.

[64] S. Elmorsy, T. Funakoshi, F. Sasazawa, M. Todoh, S. Tadano, N. Iwasaki, Chondroprotective effects of high-molecular-weight cross-linked hyaluronic acid in a rabbit knee osteoarthritis model, Osteoarthritis Cartilage 22 (1) (2014) 121–127.

[65] S. Bowman, M.E. Awad, M.W. Hamrick, M. Hunter, S. Fulzele, Recent advances in hyaluronic acid based therapy for osteoarthritis, Clin. Transl. Med. 7 (1) (2018) 1–11.

[66] P. Ghosh, D. Guidolin, Potential mechanism of action of intra-articular hyaluronan therapy in osteoarthritis: are the effects molecular weight dependent? Semin. Arthritis Rheum. 32 (1) (2002) 10–37.

[67] R.C. Gupta, R. Lall, A. Srivastava, A. Sinha, Hyaluronic acid: molecular mechanisms and therapeutic trajectory, Front. Vet. Sci. 192 (2019).

[68] M. Ishijima, T. Nakamura, K. Shimizu, K. Hayashi, H. Kikuchi, S. Soen, K. Kaneko, Intra-articular hyaluronic acid injection versus oral non-steroidal anti-inflammatory drug for the treatment of knee osteoarthritis: a multi-center, randomized, open-label, non-inferiority trial, Arthritis Res. Ther. 16 (1) (2014) 1–8.

[69] G.S. Bae, S.J. Park, The anti-inflammatory effect of *Nypa fruticans* Wurmb. fruit on lipopolysaccharide-induced inflammatory response on RAW 264.7 cells, Korea J. Herbology 31 (5) (2016) 79–84.

[70] A. Qadir, F. Shakeel, A. Ali, M. Faiyazuddin, Phytotherapeutic potential and pharmaceutical impact of *Phoenix dactylifera* (date palm): current research and future prospects, J. Food Sci. Technol. 57 (4) (2020) 1191–1204.

[71] B. Zuo, J. Zhu, F. Xiao, C. Wang, Y. Shen, X. Chen, Identification of novel biomarkers and candidate small molecule drugs in rheumatoid arthritis and osteoarthritis based on bioinformatics analysis of high-throughput data, Biosci. Rep. 40 (12) (2020).

[72] E. Sovia, J. Anggraeny, Sugar palm fruits (*Arenga pinnata*) as potential analgesics and anti-inflammatory agent, Mol. Cell. Biomed. Sci. 3 (2) (2019) 107–114.

[73] F. Li, J. Huo, Y. Zhuang, H. Xiao, W. Wang, L. Huang, Anti-nociceptive and anti-inflammatory effects of the ethanol extract of *Arenga pinnata* (Wurmb) Merr. fruit, J. Ethnopharmacol. 248 (2020), 112349.

[74] J. Tarigan, D. Barus, M.H.A. Naibaho, Synthesis of carboxymethyl polysaccharide from Arenga pinnata polysaccharide and monochloroasetic, in: Proceedings of the 1st International Conference on Chemical Science and Technology Innovation, Medan, Indonesia, July 2019, pp. 14–15.

[75] S. Sarmi, R.D. Ratnani, I. Hartati, Isolasi senyawa galaktomannan buah aren (*Arenga pinnata*) menggunakan beberapa jenis abu, Majalah Ilm. Momentum 12 (1) (2016).

[76] H. Khotimah, W. Riawan, H.A. Trisnaini, E. Zubaidah, Sugar palm fruit (*Arenga pinnata*) diminish pain and inflammatory symptoms of osteoarthritis in male Wistar rat (Rattus norvegicus), Res. J. Pharm. Technol. 11 (9) (2018) 3745–3751.

[77] Manfaat pohon aren, https://www.kompasiana.com/522018029/5b992fb143322f04de171e06/manfaat-pohon-aren (accessed on 17 September 2022)

[78] I.M. Abu Zeid, A.R.A. FarajAlla, *Borassus flabellifer* L. palmyra palm (Daleeb): biochemistry, functions and utilization, in: *Wild Fruits: Composition, Nutritional Value and* Products, Springer, Cham: Switzerland, 2019, pp. 465–479.

[79] E.R. Jansz, N. Wickremasekara, K.A.V. Sumuduni, A review of the chemistry and biochemistry of seed shoot flour and fruit pulp of the palmyrah palm (*Borassus flabellifer* L), J. Natl. Sci. Found. Sri Lanka 30 (1-2) (2002).

[80] M.S. Paschapur, M.B. Patil, R. Kumar, S.R. Patil, Influence of ethanolic extract of Borassus flabellifer L. male flowers (inflorescences) on chemically induced acute inflammation and poly arthritis in rats, Int. J. PharmTech Res. 1 (3) (2009) 551–556.

[81] Lontar bermanfaat untuk obat, https://intisari.grid.id/read/0399912/ternyata-tak-hanya-jadi-sarana-menulis-syair-atau-ajaran-agama-lontar-juga-bermanfaat-untuk-obat?page=all (accessed on 17 September 2022)

[82] M.S. Kang, K.Y. Hyun, Antinociceptive and anti-inflammatory effects of *Nypa fruticans* wurmb by suppressing TRPV1 in the sciatic neuropathies, Nutrients 12 (1) (2020) 135.

[83] S.F.R. Yahaya, N. Samsuddin, S. Mamat, R. Hod, N.Z. Abdullah, N.A.A. Rahman, S.Z.M. So'Ad, Determination of antioxidant compounds, proximate compositions and assessment of free radical scavenging activities of *Nypa fruticans* Wurmb, Sap. *Pertanika J. Sci. Technol.* 29 (3) (2021) 2061–2071.

[84] V.N. Osabor, G.E. Egbung, P.C. Okafor, Chemical profile of *Nypa fruiticans* from cross river estuary, south eastern Nigeria, Pakistan J. Nutr. 7 (1) (2008) 146–150.

[85] R. Radam, M.A. Soendjoto, A.A. Rezekiah, Ratio of filled fruit and rendement of flour produced from Nypa (*Nypa fruticans* Wurmb) fruit, J. Wetlands Environ. Manag. 9 (2) (2021) 45–53.

[86] N. Prasad, B. Yang, K.W. Kong, H.E. Khoo, J. Sun, A. Azlan, Z.B. Romli, Phytochemicals and antioxidant capacity from *Nypa fruticans* Wurmb. fruit, Evid.Based Complement. Altern. Med. 2013 (2013) 1–9.

[87] Buah nipah alternatif pemenuhan karbohidrat, https://www.republika.co.id/berita/okbpzh284/buah-nipah-alternatif-pemenuhan-karbohidrat (accessed on 17 September 2022)

[88] A. Bagherzadeh-karimi, Assessment of Effect of Topical palm Date (*Phoenix Dactylifera L.*) Preparation on Clinical Manifestation of Knee Osteoarthritis versus Diclofenac Gel: A Randomized Clinical Trial, Tabriz University of Medical Sciences, Iran, 2020. Doctoral Dissertation.

[89] F. Peyghambari, M.H. Dashti-Rahmatabadi, M.D. Rozabadi, R.D. Rozabadi, F.D. Rozabadi, M. Pangalizadeh, N. Dehghanimohammadabadi, Antinociceptive effect of palm date spathe hydroalcoholic extract on acute and chronic pain in mice as compared with analgesic effect of morphine and diclofenac, Adv. Biomed. Res. 4 (2015) 244.

[90] H.E. Kehili, S. Zerizer, K.A. Beladjila, Z. Kabouche, Anti-inflammatory effect of Algerian date fruit (*Phoenix dactylifera*), Food Agric. Immunol. 27 (6) (2016) 820–829.

[91] N.M. Deshpande, M.M. Deshpande, D. Dravyaguna, Date fruit (Phoenix dactylifera Linn) – a review on nutritional values, phytochemicals and pharmacological actions, World J. Pharmaceut. Res. 6 (8) (2017) 419–426.

[92] Manfaat pinang muda bagi kesehatan bisa tingkatkan kesuburan, https://www.merdeka.com/sumut/9-manfaat-pinang-muda-bagi-kesehatan-bisa-tingkatkan-kesuburan-kln.html (accessed on 17 September 2022)

[93] K.P. Lee, G.W. Sudjarwo, J.S. Kim, S. Dirgantara, W.J. Maeng, H. Hong, The anti-inflammatory effect of Indonesian *Areca catechu* leaf extract in vitro and in vivo, Nutr. Res. Pract. 8 (3) (2014) 267–271.

[94] K.B. Sarpangala, D. Ashwin, M. Sarpangala, Analgesic, anti-inflammatory and wound healing properties of Arecanut, *Areca catechu* L.: A review, Int. J. Ayurveda Pharm. Res. 4 (12) (2016) 78–83.

[95] P.L. Huang, C.W. Chi, T.Y. Liu, Effects of Areca catechu L. containing procyanidins on cyclooxygenase-2 expression in vitro and in vivo, Food Chem. Toxicol. 48 (1) (2010) 306–313.

[96] X. Chen, Y. He, Y. Deng, Chemical composition, pharmacological, and toxicological effects of betel nut, Evid. Based Complement. Altern. Med. (2021) 1–7.

[97] V. Jain, A. Garg, M. Parascandola, P. Chaturvedi, S.S. Khariwala, I. Stepanov, Analysis of alkaloids in areca nut-containing products by liquid chromatography-tandem mass spectrometry, J. Agric. Food Chem. 65 (9) (2017) 1977–1983.

[98] S.P. Pathak, S.S. Mathur, The component acids and glycerides of areca-nut (Areca catechu) fat, J. Sci. Food Agric. 5 (10) (1954) 461–465.

[99] C.K. Wang, W.H. Lee, Separation, characteristics, and biological activities of phenolics in areca fruit, J. Agric. Food Chem. 44 (8) (1996) 2014–2019.

[100] Manfaat mengkonsumsi buah kurma, https://rimbakita.com/pohon-kurma/https://pemkomedan.go.id/artikel-11244-manfaat-mengkonsumsi-buah-kurma.html (accessed on 17 September 2022)

[101] A.A. Karim, A.P.L. Tie, D.M.A. Manan, I.S.M. Zaidul, Starch from the sago (Metroxylon sagu) palm tree—properties, prospects, and challenges as a new industrial source for food and other uses, Compr. Rev. Food Sci. Food Saf. 7 (3) (2008) 215–228.

[102] A. Saputri, U. Amna, Z.I. Navia, Skrining fitokimia buah rumbia (metroxylon sagu rottb): studi pendahuluan pengembangan obat herbal anti hipertensi, in: Prosiding Seminar Nasional Pertanian, 2018.

[103] Tanaman sagu, https://www.kibrispdr.org/gambar-tanaman-sagu.html (accessed on 17 September 2022)

[104] P.B. Albuquerque, W. Barros Jr., G.R. Santos, M.T. Correia, P.A. Mourão, J.A. Teixeira, M.G. Carneiro-da-Cunha, Characterization and rheological study of the galactomannan extracted from seeds of *Cassia grandis*, Carbohydr. Polym. 104 (2014) 127–134.

[105] F.G. da Silva Nascimento, P.H. de Souza Ferreira Bringel, F.W.S. Maia, C.P.C. Lima, R.C. Alves, J.P.A. Feitosa, R.R. Castro, Galactomannan of Delonix regia seeds reduces nociception and morphological damage in the rat model of osteoarthritis induced by sodium monoiodoacetate, Naunyn-Schmiedeberg's Arch. Pharmacol. 394 (3) (2021) 491–501.

[106] F.D. Gunstone, Fatty Acid and Lipid Chemistry, first ed., Springer, Berlin, Jerman, 1996, pp. 1–3.

[107] E.A. Rodríguez-Leyes, V.L.G. Canavaciolo, D.M. Delange, A.R.S. Enríquez, Y.A. Fajardo, Fatty acid composition and oil yield in fruits of five Arecaceae species grown in Cuba, J. Am. Oil Chem. Soc. 84 (8) (2007) 765–767.

[108] H.L. Lopez, Nutritional interventions to prevent and treat osteoarthritis. Part I: focus on fatty acids and macronutrients, Phys. Med. Rehabil. 4 (5) (2012) S145–S154.

[109] D.A. Fritsch, T.A. Allen, C.E. Dodd, D.E. Jewell, K.A. Sixby, P.S. Leventhal, K.A. Hahn, A multicenter study of the effect of dietary supplementation with fish oil omega-3 fatty acids on carprofen dosage in dogs with osteoarthritis, J. Am. Vet. Med. Assoc. 236 (5) (2010) 535–539.

[110] J. Zhang, J. Yin, D. Zhao, C. Wang, Y. Zhang, Y. Wang, T. Li, Therapeutic effect and mechanism of action of quercetin in a rat model of osteoarthritis, J. Int. Med. Res. 48 (3) (2020), 0300060519873461.

[111] Y. Hu, Z. Gui, Y. Zhou, L. Xia, K. Lin, Y. Xu, Quercetin alleviates rat osteoarthritis by inhibiting inflammation and apoptosis of chondrocytes, modulating synovial macrophages polarization to M2 macrophages, Free Radic. Biol. Med. 145 (2019) 146–160.

[112] Y. Hu, Z. Gui, Y. Zhou, L. Xia, K. Lin, Y. Xu, Quercetin alleviates rat osteoarthritis by inhibiting inflammation and apoptosis of chondrocytes, modulating synovial macrophages polarization to M2 macrophages, Free Radic. Biol. Med. 145 (2019) 146–160.

[113] M.Y. Ansari, N. Ahmad, T.M. Haqqi, Oxidative stress and inflammation in osteoarthritis pathogenesis: role of polyphenols, Biomed. Pharmacother. 129 (2020), 110452.

[114] Z. Zhou, L. Zhang, Y. Liu, C. Huang, W. Xia, H. Zhou, X. Zhou, Luteolin protects chondrocytes from H_2O_2-induced oxidative injury and attenuates osteoarthritis

progression by activating AMPK-Nrf2 signaling, Oxid. Med. Cell. Longev. 2022 (2022) 1–20.
[115] J. Fei, B. Liang, C. Jiang, H. Ni, L. Wang, Luteolin inhibits IL-1β-induced inflammation in rat chondrocytes and attenuates osteoarthritis progression in a rat model, Biomed. Pharmacother. 109 (2019) 1586–1592.
[116] S.W. Tsai, C.C. Lin, S.C. Lin, S.P. Wang, D.H. Yang, Isorhamnetin ameliorates inflammatory responses and articular cartilage damage in the rats of monosodium iodoacetate-induced osteoarthritis, Immunopharmacol. Immunotoxicol. 41 (4) (2019) 504–512.
[117] K. Du, X. Fang, Z. Li, Ferulic acid suppresses interleukin-1β-induced degeneration of chondrocytes isolated from patients with osteoarthritis through the SIRT1/AMPK/PGC-1α signaling pathway, Immun. Inflamm. Dis. 9 (3) (2021) 710–720.
[118] X. Huang, Y. You, Y. Xi, B. Ni, X. Chu, R. Zhang, H. You, p-Coumaric acid attenuates IL-1β-induced inflammatory responses and cellular senescence in rat chondrocytes, Inflammation 43 (2) (2020) 619–628.
[119] W.N. Wan Osman, N.A. Che Ahmad Tantowi, S.F. Lau, S. Mohamed, Epicatechin and scopoletin rich *Morinda citrifolia* (Noni) leaf extract supplementation, mitigated osteoarthritis via anti-inflammatory, anti-oxidative, and anti-protease pathways, J. Food Biochem. 43 (3) (2019), e12755.
[120] R.L. Papke, N.A. Horenstein, C. Stokes, Nicotinic activity of arecoline, the psychoactive element of "Betel Nuts", suggests a basis for habitual use and anti-inflammatory activity, PLoS One 10 (10) (2015), e0140907.
[121] F.L. Liu, C.L. Chen, C.C. Lai, C.C. Lee, D.M. Chang, Arecoline suppresses RANKL-induced osteoclast differentiation in vitro and attenuates LPS-induced bone loss in vivo, Phytomedicine 69 (2020), 153195.
[122] O. Gabay, C. Sanchez, C. Salvat, F. Chevy, M. Breton, G. Nourissat, F. Berenbaum, Stigmasterol: a phytosterol with potential anti-osteoarthritic properties, Osteoarthritis Cartilage 18 (1) (2010) 106–116.
[123] N.E. Moreno-Anzúrez, S. Marquina, L. Alvarez, A. Zamilpa, P. Castillo-España, I. Perea-Arango, J. Arellano-García, A cytotoxic and anti-inflammatory campesterol derivative from genetically transformed hairy roots of *Lopezia racemosa* Cav. (Onagraceae), Molecules 22 (1) (2017) 118.
[124] W. Wang, H. Meng, Cytotoxic, anti-inflammatory and hemostatic spirostane-steroidal saponins from the ethanol extract of the roots of *Bletilla striata*, Fitoterapia 101 (2015) 12–18.
[125] L. Chen, H. Teng, Z. Xie, H. Cao, W.S. Cheang, K. Skalicka-Woniak, J. Xiao, Modifications of dietary flavonoids towards improved bioactivity: an update on structure–activity relationship, Crit. Rev. Food Sci. Nutr. 58 (4) (2018) 513–527.
[126] H. Cartika, Kimia Farmasi, Pusdik SDM Kesehatan Badan Pengembangan dan Pemberdayaan SDM Kementrian Kesehatan RI, Jakarta, Indonesia, 2016.
[127] L. Yang, L.M. Zhang, Chemical structural and chain conformational characterization of some bioactive polysaccharides isolated from natural sources, Carbohydr. Polym. 76 (3) (2009) 349–361.
[128] C. Hou, L. Chen, L. Yang, X. Ji, An insight into the anti-inflammatory effects of natural polysaccharides, Int. J. Biol. Macromol. 153 (2020) 248–255.
[129] Q. Li, Y. Feng, W. He, L. Wang, R. Wang, L. Dong, C. Wang, Post-screening characterisation and in vivo evaluation of an anti-inflammatory polysaccharide fraction from *Eucommia ulmoides*, Carbohydr. Polym. 169 (2017) 304–314.
[130] X. Xu, Y. Chang, C. Xue, J. Wang, J. Shen, Gastric protective activities of sea cucumber fucoidans with different molecular weight and chain conformations: a structure-activity relationship investigation, J. Agric. Food Chem. 66 (32) (2018) 8615–8622.
[131] Y. Shi, Q. Xiong, X. Wang, X. Li, C. Yu, J. Wu, H. Cui, Characterization of a novel purified polysaccharide from the flesh of *Cipangopaludina chinensis*, Carbohydr. Polym. 136 (2016) 875–883.
[132] G.J. Wu, S.M. Shiu, M.C. Hsieh, G.J. Tsai, Anti-inflammatory activity of a sulfated polysaccharide from the brown alga *Sargassum cristaefolium*, Food Hydrocolloids 53 (2016) 16–23.
[133] I.C. Lima, R.R. Castro, B.L. Adjafre, S.H. Sousa, D.S. de Paula, A.P.N. Alves, M.R. Mota, Galactomannan of Delonix regia seeds modulates cytokine expression and oxidative stress eliciting anti-inflammatory and healing effects in mice cutaneous wound, Int. J. Biol. Macromol. 203 (2022) 342–349.
[134] F.D.C.J. Marques, P. da Silva Pantoja, V.E.A. Matos, R.O. Silva, S.R.B. Damasceno, Á.X. Franco, P.M.G. Soares, Galactomannan from the seeds of *Caesalpinia pulcherrima* prevents indomethacin-induced gastrointestinal damage via neutrophil migration, Int. J. Biol. Macromol. 141 (2019) 68–75.
[135] M.S. Geronço, I.F. da Silveira Ramos, E.C. da Silva Filho, M. dos Santos Rizzo, A.B. Ribeiro, M.P. da Costa, Are structurally modified galactomannan derivatives biologically active? Polysaccharides 2 (1) (2021) 1–15.
[136] S.J. Maleki, J.F. Crespo, B. Cabanillas, Anti-inflammatory effects of flavonoids, Food Chem. 299 (2019), 125124.
[137] X. Wang, Y. Cao, S. Chen, J. Lin, J. Bian, D. Huang, Anti-inflammation activity of flavones and their structure-activity relationship, J. Agric. Food Chem. 69 (26) (2021) 7285–7302.
[138] J. González-Gallego, M.V. García-Mediavilla, S. Sánchez-Campos, M.J. Tuñón, Fruit polyphenols, immunity and inflammation, Br. J. Nutr. 104 (S3) (2010) S15–S27.
[139] Z. Sroka, A. Sowa, A. Dryś, Inhibition of lipoxygenase and peroxidase reaction by some flavonols and flavones: the structure-activity relationship, Nat. Prod. Commun. 12 (11) (2017), 1934578X1701201111.
[140] G. Odontuya, J.R.S. Hoult, P.J. Houghton, Structure-activity relationship for antiinflammatory effect of luteolin and its derived glycosides, Phytother Res. 19 (9) (2005) 782–786.
[141] A. Turkiewicz, I.F. Petersson, J. Björk, G. Hawker, L.E. Dahlberg, L.S. Lohmander, M. Englund, Current and future impact of osteoarthritis on health care: a population-based study with projections to year 2032, Osteoarthritis Cartilage 22 (11) (2014) 1826–1832.
[142] K. Sinusas, Osteoarthritis: diagnosis and treatment, Am. Fam. Physician 85 (1) (2012) 49–56 [PMID:22230308].
[143] I.C. Lima, R.R. Castro, B.L. Adjafre, S.H. Sousa, D.S. de Paula, A.P.N. Alves, M.R. Mota, Galactomannan of Delonix regia seeds modulates cytokine expression and oxidative stress eliciting anti-inflammatory and healing effects in mice cutaneous wound, Int. J. Biol. Macromol. 203 (2022) 342–349.
[144] R.R. Castro, C.M.M. Silva, R.M. Nunes, P.L. Cunha, R.C.M. de Paula, J.P. Feitosa, F.A. Rocha, Structural characteristics are crucial to the benefits of guar gum in experimental osteoarthritis, Carbohydr. Polym. 150 (2016) 392–399.