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Review paper

Anti-inflammatory and analgesic properties of Moroccan medicinal plants: Phytochemistry, *in vitro* and *in vivo* investigations, mechanism insights, clinical evidences and perspectives

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ABSTRACT

Moroccan medicinal plants exhibit several pharmacological properties such as antimicrobial, anticancer, antidiabetic, analgesic, and anti-inflammatory effects, which are related to the presence of numerous bioactive compounds, including phenolic acids, flavonoids, and terpenoids. In the present review, we systematically evaluate previously published reports on the anti-inflammatory and analgesic effects of Moroccan medicinal plants. The in vitro investigations revealed that Moroccan medicinal plants inhibit several enzymes related to inflammatory processes, whereas in vivo studies noted significant anti-inflammatory and analgesic effects as demonstrated using different experimental models. Various bioactive compounds exhibiting in vitro and in vivo anti-inflammatory and analgesic effects, with diverse mechanisms of action, have been identified. Some plants and their bioactive compounds reveal specific secondary metabolites that possess important anti-inflammatory effects in clinical investigations. Our review proposes the potential applications of Moroccan medicinal plants as sources of anti-inflammatory and analgesic agents.

1. Introduction

Inflammation is a physiological process that involves the intervention of the immune system. The key role of inflammation is to protect organisms against microbial infections, and in some instances, it acts as a physiological defense mechanism against certain diseases such as cancer [1]. However, under certain circumstances, inflammation can become harmful, leading to serious pathological conditions. The prolonged overexpression of inflammatory factors can alter several physiological processes by activating numerous signaling pathways, especially the transcriptional factor nuclear factor kappa B (NF-κB), which regulates the expression of multiple inflammatory genes that induce the inflammatory process [2]. Cellular inflammation can be the driving factor for several diseases, leading to cell death and organ damage, or cellular stimulation, thus initiating tumor formation. Chronic inflammation is considered as an integral part of developing various diseases, including diabetes, heart diseases, cancer, digestive disorders, autoimmune diseases, or neurodegenerative disorders [3,4]. Accordingly, the suppression of inflammation is an attractive therapeutic strategy to fight inflammation-related diseases. However, drugs targeting inflammation, such as nonsteroidal anti-

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inflammatory drugs (NSAIDs), demonstrate serious side effects on human health [5]. To meet the need for efficacious anti-inflammatory drugs that can overcome the debilitating side effects of currently available medications, scientists have directed their efforts toward identifying safe and effective anti-inflammatory agents from herbal medicines.

Over the past decade, several studies have focused on identifying natural bioactive compounds with anti-inflammatory and analgesic effects. Secondary metabolites of medicinal plants, including polyphenols, flavonoids, terpenoids, and alkaloids, are essential sources for developing anti-inflammatory and analgesic drugs [6–8]. Recent reports have revealed that these molecules exhibit an anti-inflammatory effect by suppressing inflammatory mediators involved in inflammatory processes, including cytokines, chemokines, and pro- and neo-inflammatory mediators [9].

Notably, there exist numerous examples of successful drug development from medicinal plants. Morphine was discovered from natural sources and remains one of the most potent analgesic drugs for pain management. Morphine was isolated from poppy latex (*Papaver somniferum*), more commonly known as opium, and possesses sedative and analgesic properties [10]. Typically, analgesics can be categorized as morphine and non-morphine analgesics. Morphine and its derivatives are selective, are commonly known as opiates, and demonstrate various psychotropic properties, including a central depressant effect. Non-morphine derivatives present analgesic and antipyretic or anti-inflammatory activities and are prescribed for low-intensity pain. Morphine analgesia suppresses painful sensations through specific signaling pathways and is used for treating chronic pain, hyperalgesia, hepatic and renal colic, myocardial infarction, acute lung edema, and postoperative pain [11]. However, these analgesics present several side effects, including addiction, nausea, constipation, and respiratory depression. In an attempt to overcome some side effects associated with morphine, numerous semisynthetic derivatives have been developed, including codethyline, pholcodine, and diamorphine, as well as synthetic products such as pethidine, phenoperidine, and buprenorphine [12].

In Morocco, medicinal plants have been used since antiquity to treat illnesses such as diabetes, microbial infections, cancer, and inflammation [13]. Studies have reported that products extracted from these medicinal plants exhibit important pharmacological properties such as antibacterial, anticancer, antidiabetic, and anti-inflammatory effects and can be potentially developed into new drugs targeting human and animal diseases. In the present review, the in vitro and in vivo anti-inflammatory and analgesic reports on Moroccan medicinal plants are summarized and critically analyzed to provide a clear perspective on their potential applications in developing novel drugs with potent activity and improved safety profiles.

2. Anti-inflammatory activities

2.1. In vitro anti-inflammatory effects

Lipoxygenase (LOX) is an enzyme that catalyzes the addition of molecular oxygen to fatty acids containing a *cis,cis*-1,4-pentadiene system originating from unsaturated fatty acid hydroperoxides [14]. The products possess an oxidant-promoting effect, and therefore, anti-LOXs are deemed as antioxidants. LOX products can also be converted to other derivatives that play crucial roles in inflammatory processes. Thus, the suppression of LOX activity can reduce inflammatory symptoms. Cyclooxygenase (COX) catalyzes the degradation of eicosatrienoic acid (arachidonic acid) into several leukotrienes [14]. Researchers have attempted to develop novel and more efficient anti-inflammatory drugs by inhibiting COX activity. Some Moroccan medicinal plants reportedly possess the ability to significantly inhibit LOX. Table S1 [15, 16] summarizes the findings of studies assessing the inhibitory effects of Moroccan medicinal plants on LOX.

Miguel et al. [15] evaluated the anti-LOX effect of hydro-alcoholic extracts of *Haloxylon scoparium*, *Corrigiola telephiifolia*, *Ammodaucus leucotrichus*, *Chamaerops humilis*, *Sideritis arborescens*, *Ammi visnaga*, *Vitex agnus castus*, *Retama raetam*, *Berberis vulgaris*, *Viscum album*, and *Equisetum arvense*. The results revealed that all tested species exhibited anti-LOX activity with some variability. Extracts of *V. album*, *B. vulgaris*, and *A. visnaga* demonstrated the most potent LOX inhibitory activity, with IC_{50} values of 0.236 ± 0.030, 0.266 ± 0.030, and 0.262 ± 0.030 mg/mL, respectively. Despite the high activity, these effects were significantly inferior to the inhibitory effect demonstrated by the positive control (nordihydroguaiaretic acid; IC_{50} value of 0.020 ± 0.030 mg/mL) [15]. The authors revealed that the inhibition of LOX by plant extracts was positively correlated with their antioxidant activities [15,16].

In another study, Aazza et al. [16] evaluated the LOX inhibitory effect of *Thymus vulgaris*, *Citrus limon*, *Citrus aurantium*, *Eucalyptus globulus*, *Cupressus sempervirens*, and *Foeniculum vulgare* essential oils. They reported that the essential oils extracted from *F. vulgare* presented the most potent inhibitory effect at the lowest concentration value (IC_{50}=0.04 ± 0.01 mg/mL). The essential oils of *E. globulus* (IC_{50}=0.16 ± 0.07 mg/mL), *C. sempervirens* (IC_{50}=0.17 ± 0.07 mg/mL), and *T. vulgaris* (IC_{50}=0.19 ± 0.00 mg/mL) showed unexpected anti-LOX activities [16].

2.2. In vivo anti-inflammatory effects

The inhibition and/or the suppression of inflammation is one of the most important strategies to treat several complicated pathologies such as cancer, diabetes, and atherosclerosis. Several bioactive compounds have been utilized to specifically target inflammatory mediators and signaling pathways leading to this process. However, these anti-inflammatory drugs are accompanied by serious side effects, especially hepatotoxicity. Numerous studies have evaluated the anti-inflammatory activity of secondary metabolites from terrestrial plants. In Morocco, several research groups examined the in vivo anti-inflammatory activity of extracts derived from endogenous medicinal plants and their isolates (Table 1) [17–31]. As listed in Table 1, Moroccan medicinal plants such as *Meiocarpidium lepidotum*, *Asphodelus aestivus*, *Calendula arvensis*, *Cistus salviifolius*, *Cistus monspeliensis*, *Tetraclinis articulata*, *Ceratonia siliqua*, *Pelargonium graveolens*, *Marrubium vulgare*, *Melissa officinalis*, *Syzygium aromaticum*, *Papaver rhoeas*, *Delphinium staphysagria*, *Ziziphus lotus*, *Argania spinosa*, and *Zygophyllum gaetulum* have been investigated. These plants belong to several plant families, including Annonaceae, Asphodelaceae, Asteraceae, Cistaceae, Cupressaceae, Fabaceae, Geraniaceae, Lamiaceae, Myrtaceae, Papaveraceae, Ranunculaceae, Rhamnaceae, Sapotaceae, and Zygophyllaceae.

2.2.1. In vivo anti-inflammatory activity of extracts

Moroccan medicinal plant extracts are rich in secondary metabolites such as phenolic acids, flavonoids, and alkaloids. These compounds are well-known for their anti-inflammatory effect. Previous literature has revealed that Moroccan medicinal plant extracts possess a potent anti-inflammatory effect, confirmed in several in vivo assays (Table 1). Meddah et al. [17] evaluated the anti-inflammatory effect of *M. lepidotum* (Annonaceae), a medicinal plant used in Moroccan traditional medicine to treat several illnesses [17]. The in vivo anti-inflammatory effect of *M. lepidotum* crude aqueous extract was evaluated at 1, 10, and 100 mg/kg doses using carrageenan-induced hyperalgesia by injecting 50 μL of λ-carrageenan (2.5%) suspended in saline (0.9%) into the plantar

Table 1
In vivo anti-inflammatory activity of Moroccan medicinal plants.

Family	Plant	Parts	Extract/ Compound	Doses	Administration	Model	Effects	Refs.
Annonaceae	*Meiocarpidium lepidotum*	Stems and barks	Aqueous extract	1, 10, and 100 mg/kg	Oral	Carrageenan-induced hyperalgesia (inflammation model) in mice	Anti-inflammatory effect similar to that obtained with 150 mg of acetylsalicylic acid and 10 mg of indomethacin	[17]
Asphodelaceae	*Asphodelus microcarpus*	Leave, fruits, and roots	Methanol extract	100 and 200 mg/kg	Oral	Carrageenan- and experimental trauma-induced rat paw edema	Significant anti-inflammatory effect at 200 mg/kg with all three extracts	[18]
Asteraceae	*Calendula arvensis*	Flowers	Methanol, aqueous, and hexane extracts	300 and 500 mg	Oral	Carrageenan- and experimental trauma-induced hind paw edema in rats	Significant reduction and inhibition of edema (carrageenan-induced) of 51.08% and 71.33% at doses of 300 and 500 mg/kg hexane extracts, respectively Significant reduction and inhibition of edema (trauma-induced) of 63.38% and 76.33% at doses of 300 and 500 mg/kg hexane extracts, respectively	[19]
Cistaceae	*Cistus salviifolius*	Aerial parts	Aqueous extract	500 mg/kg of body weight	Oral	Carrageenan-induced paw edema assay in rats	Significant inhibition of paw edema (85.78% ± 0.64%)	[20]
Cistaceae	*Cistus monspeliensis*	Aerial parts	Aqueous extract	500 mg/kg of body weight	Oral	Carrageenan-induced paw edema assay in rats	Significant inhibition of paw edema (91.57% ± 0.52%)	[20]
Cupressaceae	*Tetraclinis articulata*	Leaves	Essential oils	200 mg/kg	Oral	Carrageenan- and trauma-induced rat paw edema	Essential oils demonstrated an effective reduction in swelling by 64.71% ± 9.38% and 69.09% ± 6.02%	[21]
Fabaceae	*Ceratonia siliqua*	Barks	Methanol extract	50, 100, and 200 mg/kg	Oral	Carrageenan- and experimental trauma-induced hind paw edema in rodents	Significant reduction and inhibition of edema comparable to the reference drug (indomethacin) used in both models	[22]
Myrtaceae	*Syzygium aromaticum*	Aerial parts	Essential oils	250 mg/kg	Oral	Carrageenan-induced hyperalgesia (inflammation model) in mice	The edema size, at 90 min after carrageenan injection, was reduced to 12.77% and was progressively reduced to 7.49% at 3 h and to 3.45% at 6 h	[23]
Lamiaceae	*Marrubium vulgare*	Whole plant	Methanol extract	100 and 200 mg/kg	Oral	Carrageenan-and PGE_2-induced hind paw edema model	Significant inhibition, at 200 mg/kg, of 34.0% and 23.2%–27.2% of carrageenan- and PGE_2-induced hind paw edema, respectively, compared to the reference drug (38%)	[24]
Lamiaceae	*Melissa officinalis*	Leaves	Essential oils	200 and 400 mg/kg	Oral	Carrageenan- and experimental trauma-induced hind paw edema in rats	Significant inhibition of 61.76% at 6 h and 91.66% at 3 h (200 mg/kg) in carrageenan- and trauma-induced hind paw edema, respectively, compared with the reference drug (52.94%) Significant inhibition of 70.58% at 6 h and 94.44% at 3 h (400 mg/kg) in carrageenan- and trauma-induced hind paw edema, respectively, compared with the reference drug (52.94%)	[25]
Geraniaceae	*Pelargonium graveolens*	Aerial parts	Essential oils	250 mg/kg	Oral	Carrageenan-induced hyperalgesia (inflammation model) in mice	Decreased edema development by 18.90%, 12.68%, and 13.01% after 90 min, 3 h, and 6 h following carrageenan injection, respectively	[23]
Papaveraceae	*Papaver rhoeas*	Aerial parts	Aqueous extract	400 and 800 mg/kg	Oral	Carrageenan-induced rat paw edema	Inhibited inflammation by 87.47%, 86.99%, and 75.65% (400 mg/kg) at 90 min, 3 h, and 6 h, respectively	[26]
						Experimental trauma-induced rat paw edema	Inhibited inflammation by 87.47%, 87.49%, and 83.61% (800 mg/kg) at 90 min, 3 h, and 6 h, respectively	
Ranunculaceae	*Delphinium staphysagria*	Seeds	Alkaloid extract	20 and 40 mg/kg	Oral	Carrageenan- and experimental trauma-induced rat paw edema	A significant reduction, at 20 mg/kg, of 71.4% (carrageenan) and 64.7% (traumatism) in paw volume compared to indomethacin (10 mg/kg)	[27]
Rhamnaceae	*Ziziphus lotus*	Seeds	Essential oils	200 and 300 mg/kg	Oral	Carrageenan-induced paw edema and experimental trauma-induced inflammatory hind paw edema	Inhibited carrageenan-induced paw edema by 64.33% and 88.72% at 200 and 300 mg/kg, respectively, compared with indomethacin (88.84%) Inhibited experimental trauma-induced paw edema by 43.40% and 86.82% at 200 and 300 mg/kg, respectively, compared with indomethacin (70.50%)	[28]
Sapotaceae	*Argania spinosa*	Seeds	Oil	300 and 500 mg/kg	Oral	Carrageenan- and experimental trauma-induced paw edema	Reduced edema in the first and second phases of carrageenan inflammation	[29]
Zygophyllaceae	*Zygophyllum gaetulum*	Aerial parts	Aqueous extract	500 mg/kg	Oral	Carrageenan-induced hyperalgesia (inflammation model) in mice	Reduced paw volume (47.48%), compared with indomethacin (82.46%)	[30]

(*continued on next page*)

Table 1 (*continued*)

Family	Plant	Parts	Extract/ Compound	Doses	Administration	Model	Effects	Refs.
Zygophyllaceae	*Zygophyllum gaetulum*	Aerial parts	Ethanolic extract	500 mg/ kg	Oral	Carrageenan-induced hyperalgesia (inflammation model) in mice	Reduced paw volume (46%), compared with indomethacin (82.46%)	[30]
Zygophyllaceae	*Zygophyllum gaetulum*	Aerial parts	Aqueous extract	500 mg/ kg	Oral	Carrageenan-induced hyperalgesia (inflammation model) in mice	Reduced paw volume (47.40%), at 90 min, compared with indomethacin (82.46%)	[31]

surface of the right mouse hind paw. The paw volume was measured 1, 2, 3, and 4 h after injection using an LE 7500 plethysmometer. The results showed that *M. lepidotum* extract significantly reduced the swelling of edematous paws. The anti-inflammatory effect was similar to the effects demonstrated by acetylsalicylic acid (150 mg) and indomethacin (10 mg). The authors attributed the observed anti-inflammatory effect to the presence of triterpenes as the major class of compounds in the *M. lepidotum* crude aqueous extract [17].

In another study, Hosni et al. [18] investigated the anti-inflammatory effect of the leaves, fruits, and roots of *Asphodelus microcarpus* (Asphodelaceae) methanolic extracts. In this study, the extracts were orally administered at 100 and 200 mg/kg, and carrageenan-induced rat paw edema was established by subcutaneously injecting 0.05 mL of 1% carrageenan in NaCl (9%) into the subplate area of the left rat paw. The experimental trauma-induced rat paw edema was assayed by dropping a 50 g weight on the left rat paw. Then, the volume of both paws was measured using a plethysmometer after 90 min, 3 h, and 6 h. The results revealed that *A. microcarpus* extracts possessed a significant anti-inflammatory effect at 200 mg/kg. The leaf extract showed potent inhibition (80.77%) when compared with indomethacin, which was employed as the positive control (79.41%). The toxicological investigation revealed that this plant was non-toxic at the specified doses.

By employing identical methods (carrageenan- and experimental trauma-induced hind paw edema), Abudunia et al. [19] evaluated the anti-inflammatory effect of *C. arvensis* methanol, aqueous, and hexane extracts. This study revealed that *C. arvensis* extracts exhibited potent anti-inflammatory activity. The hexane extract showed potent effects at doses of 300 and 500 mg/kg. Three hours after edema induction, the extract (300 mg/kg) reduced carrageenan-induced edema by 51.08% and experimental trauma-induced rat paw edema by 71.33%; at 500 mg/kg, the reduction was 63.38% and 76.33%, respectively, in both assays. These results were similar to those of indomethacin, the standard drug, which showed a 72.36% reduction in edema [19].

C. salviifolius (L.) and *C. monspeliensis* (L.), two medicinal plants belonging to the Lamiaceae family, are used in Moroccan folk medicine to treat several illnesses, especially inflammatory-related diseases. To validate their anti-inflammatory effect, Sayah et al. [20] evaluated the in vivo anti-inflammatory effect of aqueous extracts of these two plants (aerial parts) using the carrageenan-induced paw edema assay in rats. The results revealed that aqueous extracts of *C. salviifolius* and *C. monspeliensis* significantly inhibited paw edema at 500 mg/kg, resulting in inhibition values of 85.78% ± 0.64% and 91.57% ± 0.52%, respectively, when compared with the reference drug indomethacin (10 mg/kg), which presented an inhibition value of 62.75% ± 1.21% [20].

The methanolic bark extract of *C. siliqua* L., a medicinal plant used in Morocco as an antidiarrheal and diuretic, was evaluated for its anti-inflammatory effect. The effect of this extract (50, 100, and 200 mg/kg per oral (p.o.)) was assessed in female Swiss mice (20–30 g) and male Wistar rats (150–250 g) by inducing edema of the hind paw using carrageenan and physical trauma [22]. The findings revealed that the *C. siliqua* methanolic bark extract exhibited a maximal reduction (0.20 ± 0.01) and inhibition (68.70%) of edema at 200 mg/kg, similar to that of indomethacin (0.19 ± 0.01 and 71%), in carrageenan-induced rat paw edema. In the experimental trauma-induced paw edema model, the extract inhibited edema formation by 70%, with a reduction of 0.20 ± 0.01, similar to indomethacin, which presented 74.3% inhibition and 0.18 ± 0.0 reduction in edema [22]. A toxicological investigation demonstrated that *C. siliqua* extracts did not induce mortality or alter animal behavior [22].

The anti-inflammatory activity of *M. vulgare* methanolic extract was evaluated by employing carrageenan- and prostaglandin E2 (PGE_2)-induced hind paw edema models [24]. The results revealed that this extract demonstrated significant inhibition (34.0%) at 200 mg/kg in the carrageenan-induced hind paw edema test. Interestingly, the extract (200 mg/kg) showed considerable inhibition (23.2%–27.2%) in PGE_2-induced hind paw edema when compared with the reference drug (indomethacin), which showed 38% inhibition after 45 min. However, the inhibitory activity of the *M. vulgare* extract was significantly lower than that of *C. siliqua* extracts [24].

P. rhoeas L. (Papaveraceae) flowers are used to treat mild earache, toothache, and neuralgia. Hajjaj et al. [26] evaluated the anti-inflammatory effect of an aqueous extract of *P. rhoeas* (400 and 800 mg/kg p.o.) by inducing hid-paw edema using carrageenan and physical trauma. The *P. rhoeas* aqueous extract (400 mg/kg) exhibited inhibition of 87.47%, 86.99%, and 75.65% at 90 min, 3 h, and 6 h, respectively, in carrageenan-induced hind paw edema. However, at 800 mg/kg, the aqueous extract showed inhibition of 87.47%, 87.49%, and 83.61%, respectively, in experimental trauma-induced rat paw edema. This plant exhibited no toxicity at investigated doses (LD_{50}=2000 mg/kg) [26].

Faridi et al. [27] evaluated the anti-inflammatory effect of *D. staphysagria* seed extracts, reportedly rich in alkaloids, by employing carrageenan-induced rat paw edema and an experimental trauma model by dropping a 50 g weight on the rat paw. The authors revealed that oral administration of *D. staphysagria* alkaloid extracts (20 mg/kg) significantly reduced paw volume by 71.4% (carrageenan) and 64.7% (traumatism) when compared with indomethacin as the drug control [27].

Z. gaetulum Emberger. & Maire. is a medicinal plant used in Moroccan traditional medicine to combat inflammation, diabetes, spasms, and diarrhea. Experimental studies have revealed the anti-inflammatory effect of this species [28].

Animals treated with an aqueous extract of *Z. gaetulum* demonstrated a significant inhibition in edema in all phases of the experiment, with inhibitions of 47.40%, 33.94%, and 11.04% at 90 min, 3 h, and 6 h, respectively, compared with the reference drug (indomethacin) presenting inhibitions of 82.46%, 31.67%, and 18.24%, respectively [31]. The anti-inflammatory effect of *Z. gaetulum* ethanolic and aqueous extracts was evaluated by Ait El Cadi et al. [30] by employing carrageenan-induced hyperalgesia in mice. Oral administration of these extracts at 500 mg/kg potently

inhibited edema in the last phase of the experimental model. The paw volume significantly reduced following treatment with the ethanolic and aqueous extracts, presenting inhibitions of 46% and 47.48%, respectively, compared with indomethacin (positive control), which showed 82.46% inhibition [30].

2.2.2. In vivo anti-inflammatory activity of the volatile compounds

Essential oils are known to contain several compounds such as monoterpenes, sesquiterpenes, and other components that demonstrate numerous beneficial biological effects. Studies have reported various essential oils isolated from Moroccan medicinal plants such as *T. articulata*, *P. graveolens*, *M. officinalis*, *S. aromaticum*, *Z. lotus*, and *Z. gaetulum,* which were investigated for their anti-inflammatory properties, as presented in Table 1.

T. articulata (known as Al'Araar) is a Moroccan medicinal plant used for treating diarrhea, gastric pain, and diabetes. In a recent study, El Jemli et al. [21] investigated the anti-inflammatory effect of the essential oil from *T. articulata* leaves (200 mg/kg) by inducing rat paw edema via carrageenan and physical trauma. The authors revealed that essential oils derived from *T. articulata* significantly reduced swelling by 64.71% ± 9.38% and 69.09% ± 6.02% in the chemical and mechanical methods, respectively, when compared with the effect of indomethacin as a reference drug, presenting inhibitions of 62.37% and 75.45%, respectively. These results were attributed to the presence of bornyl acetate (26.81%), camphor (22.40%), and α-pinene (7.16%) as major bioactive compounds of *T. articulata* essential oil. In addition, no mortality was observed on investigating the acute toxicity of this essential oil (LD_{50}=5000 g/kg).

M. officinalis is another medicinal plant belonging to the Lamiaceae family. In Morocco, this plant is used as a calming, antispasmodic, and muscle-strengthening agent. Essential oils from the leaves of this plant were evaluated for their anti-inflammatory properties using carrageenan- and experimental trauma-induced hind paw edema in rats [25]. The results revealed that *M. officinalis* essential oils, administered at 200 and 400 mg/kg p.o., showed a significant reduction and inhibition of edema by 70.58% and 76.47%, respectively, at 90 min, and by 61.76% and 70.58% at 6 h, in carrageenan-induced hind paw edema. The results were comparable with the positive control (indomethacin), which demonstrated 76.47% and 52.94% inhibition after 1 h and 3 h, respectively. In the experimental trauma model, *M. officinalis* essential oil at 200 and 400 mg/kg p.o. exhibited maximum *anti*-inflammatory activity, with 91.66% and 94.44% edema inhibition after 3 h, respectively. After 6 h, the inhibition was similar to that observed with indomethacin (10 mg/kg, p.o.), revealing an inhibition of 91.66%. This effect could be attributed to the presence of nerol, citral, isopulegol, caryophyllene, caryophyllene oxide, and citronella as major compounds of *M. officinalis* essential oil [25].

Marmouzi et al. [23] reported the anti-inflammatory effect of essential oils of *P. graveolens* (Geraniaceae) and *S. aromaticum* (Myrtaceae) aerial parts by employing the carrageenan model at 250 mg/kg. For *S. aromaticum*, the edema size of the group treated with essential oil was reduced to 12.77%, 90 min after the carrageenan injection. This value was reduced to 7.49% and 3.45% after 3 h and 6 h, respectively. Regarding *P. graveolens* essential oil, edema development 90 min after carrageenan injection was progressively reduced to 12.68% at 3 h and 13.01% at 6 h. The combination of both essential oils showed a considerable anti-inflammatory activity, with an inhibition of 86.17%, 87.79%, and 84.84% produced at 90 min, 3 h, and 6 h, respectively. The results were comparable with the reduction produced by 10 mg/kg and 20 mg/kg of indomethacin at 90 min, 3 h, and 6 h, which presented inflammation inhibition values ranging 71.17%–86.89%, 78.59%–83.94%, and 67.63%–75.63%, respectively [23]. The chemical analysis of these essential oils revealed the presence of eugenol (74.06%), caryophyllene (11.52%), and carvacrol acetate (7.82%) as major compounds of *S. aromaticum*. Citronellol (30.77%), 10-*epi*-γ-eudesmol (22.59%), and geraniol (13.95%) were the major compounds identified in *P. graveolens* [23].

In Morroco, *Z. lotus* is a medicinal plant used as an anti-inflammatory, antidiabetic, and antimicrobial agent. El Hachimi et al. [28] examined the anti-inflammatory effect of *Z. lotus* seed essential oil using carrageenan-induced paw edema and trauma-induced inflammatory hind paw edema. Like indomethacin (used as the reference drug), *Z. lotus* essential oil exhibited potent anti-inflammatory activity. At a dose of 300 mg/kg p.o., this oil exhibited a potent dose-dependent effect, revealing a better inhibitory effect than that of indomethacin [28]. The authors suggested that this plant could be considered as a promising source of anti-inflammatory agents as it showed no toxicity in animal models.

3. Analgesic activity

Medicinal plants have been used since ancient times as analgesic agents. As synthetic drugs are expensive and have several side effects, plants are considered alternative sources for screening analgesic drugs. Medicinal plants are known to induce a biological balance owing to their natural active ingredients, synergistic effects of active ingredients, and low levels of accumulation in the body. Drugs and their side effects are among the main reasons why pharmaceutical companies and the public adopt herbal medicines to treat certain diseases. Plants and their products can be used in some instances as ideal substitutes for synthetic drugs [32]. Research on plants with medicinal properties, including analgesic activities, is necessary and can serve as a basis for treating various disorders and complications [33]. Flavonoids, alkaloids, and several other chemical classes have proven useful as analgesic agents. Flavonoids are among the most abundant chemical classes of medicinal plants and have revealed important analgesic activities. Indeed, flavonoids reportedly prevent prostaglandins from inducing COX in inflamed tissues [32]. Apigenin is known to reduce the flow of lipids needed to signal pain. Therefore, flavonoids reduce inflammatory pain by inhibiting receptors and signaling cascades [32].

The analgesic activity of Moroccan medicinal plants was investigated by several research groups [12,17,18,20,24,34–38]. Numerous medicinal plants have been assessed, including *M. vulgare*, *M. lepidotum*, *Nepeta amethystina*, *C. monspeliensis*, *C. salviifolius*, *Cotula cinerea*, *P. rhoeas*, *A. microcarpus*, *Chenopodium ambrosioides*, *Nepeta atlantica*, *Nepeta tuberosa*, and *Thymus broussonetii*, belonging to six botanical families, including Labiaceae, Papaveraceae, Asteraceae, Cistaceae, Lamiaceae, and Annonaceae (Table 2) [12,17,20,24,26,34–39].

Among medicinal plants evaluated from the Lamiaceae family, Belabda et al. [36] assessed the analgesic effect of the methanol extract of *N. amethystina* aerial parts using abdominal writhing and tail-flick tests following intraperitoneal (i.p.) administration of 25 and 50 mg/kg doses. Accordingly, the extract showed significant peripheral and central analgesic effects. The peripheral analgesic effect was higher than that demonstrated by acetylsalicylic acid, which was used as a standard drug at 200 mg/kg i.p. Additionally, the central analgesic activity of *N. amethystina* was significantly comparable with that of morphine (50 mg/kg i.p.) [36]. *M. vulgare*, another medicinal species in the Lamiaceae family, is traditionally used as an anti-inflammatory and analgesic agent. The analgesic effect of this herb was evaluated using the abdominal writhing test [24]. Accordingly, the methanol extract of the aerial parts, administered orally at 100 and 200 mg/kg, exhibited moderate peripheral analgesic activity [24].

Table 2
Moroccan plant extracts investigated for their analgesic activity.

Species	Used parts	Extract tested	Doses	Route of administration	Method	Effects	Refs.
Asphodelus microcarpus (Labiaceae)	Leaves	Methanol	25, 50, and 100 mg/kg	Oral	Writhing, tail flick	A significant analgesic effect for writhing test	[39]
Papaver rhoeas (Papaveraceae)	Leaves	Water	200 and 400 mg/kg	Intraperitoneal	Writhing, tail flick	A significant analgesic effect for both methods used	[26]
Cotula cinerea (Asteraceae)	Aerial parts	Essential oils, hexane, ethyl acetate, *n*-butanol	500 mg/kg	Oral	Tail flick, hot plate	Stronger central analgesic effect when compared with morphine	[38]
Cistus salviifolius (Cistaceae)	Aerial parts	Aqueous extract	500 mg/kg	Intraperitoneal	Writhing, tail flick	A significant analgesic effect observed with both methods employed	[20]
Cistus monspeliensis (Cistaceae)	Aerial parts	Aqueous extract	500 mg/kg	Intraperitoneal	Writhing, tail flick	A significant analgesic effect observed with both methods employed	
Nepeta amethystina (Lamiaceae)	Aerial parts	Methanol extract	25 and 50 mg/kg	Intraperitoneal	Writhing, tail flick	Potent analgesic effect (dose-dependent) Stronger central analgesic effect when compared with morphine at 50 mg/kg	[36]
Myocardium lepidotum (Annonaceae)	Whole plant	Aqueous extract	1, 10, and 100 mg/kg	Oral	Writhing, tail flick	Analgesic effect similar to the positive control, morphine	[17]
Marrubium vulgare (Lamiaceae)	Whole plant	Methanol extract	100 and 200 mg/kg	Oral	Writhing	Moderate analgesic activity	[24]
Chenopodium ambrosioides (Lamiaceae)	Leaves	Aqueous extract	100, 200, and 300 mg/kg	Oral	Writhing, hot plate	A significant analgesic effect with both methods employed	[37]
Nepeta atlantica (Lamiaceae)	Aerial parts	Hexane, dichloromethane	60 mg/kg	Intraperitoneal	Tail flick, writhing	Significant central analgesic effect with both extracts Maximum peripheral analgesic effect with hexane extract	[12]
Nepeta Tuberosa (Lamiaceae)	Aerial parts	Ethyl acetate, butanol	60 mg/kg	Intraperitoneal	Tail flick, writhing	Significant central analgesic effect for both extracts Maximum peripheral analgesic effect for hexane extract	[12]
Thymus broussonetii (Lamiaceae)	Leaves and stems	Water, butanol ethyl acetate	50, 100, 200, and 300 mg/kg	Intraperitoneal and Oral	writhing Tail flick, writhing, hot plate	Significant antinociceptive activity with aqueous and butanol extracts Better analgesic effect (central and peripheral) with the aqueous extract	[35]
Cotula cinerea (Asteraceae)	Whole plant	Ethyl ether, ethyl acetate, and *n*-butanol	100 mg/kg	Oral	Writhing	Significant analgesic effect with ethyl ether extract	[34]

In another report, Bouidida et al. [12] investigated the analgesic effect of *N. atlantica* and *N. Tuberosa* (two medicinal species of Lamiaceae). For *N. atlantica*, the authors used hexane and dichloromethane extracts, while ethyl acetate and butanol extracts of *N. Tuberosa* were employed. The analgesic activity was investigated by i.p. administration of each extract at 60 mg/kg using the tail-flick and writhing tests. Both dichloromethane and ethyl acetate extracts demonstrated significant central analgesic effects. The results revealed that extracts of both medicinal plants showed important analgesic activity, with few differences. The hexane extract of *N. atlantica* exhibited the most potent peripheral analgesic effect.

The aqueous extract of *C. ambrosioides* leaves (Lamiaceae) was evaluated for its analgesic activity by Hallal et al. [37] by employing writhing and hot plate tests. After oral administration of 100, 200, and 300 mg/kg, this extract exhibited a potent analgesic effect in both models. Using models such as formalin injection, tail-flick test, abdominal writhing, and hot plate test, Elhabazi et al. [35] evaluated the analgesic effect of *T. broussonetii* water, butanol, and ethyl acetate extracts at 50, 100, 200, and 300 mg/kg. Following oral and i.p. administration, the results revealed that butanol and aqueous extracts exhibited antinociceptive activity. This effect was observed at both central and peripheral levels.

C. cinerea (Asteraceae) is a medicinal plant used in Morocco to treat several illnesses, including inflammation. In 1999, Markouk et al. [34] investigated the analgesic effect of ethyl ether, ethyl acetate, and *n*-butanol whole plant extracts using the writhing test. The administration (p.o.) of these three extracts at 100 mg/kg revealed that only the ethyl ether extract exhibited significant analgesic activity. The essential oil, hexane, ethyl acetate, and *n*-butanol aerial part extracts of the same plant were recently assessed for their central and peripheral analgesic effects using the tail-flick and hot plate tests [38]. The results revealed that the extracts exhibited potent analgesic activity, especially on the central nervous system, which was significantly comparable with that of morphine (used as the standard drug). Sayah et al. [20] evaluated the analgesic activity of aqueous extracts derived from the aerial parts of two species of genus *Cistus* (*C. salviifolius* and *C. monspeliensis*) using writhing and tail-flick tests, at 500 mg/kg i.p. Both plants showed a significant analgesic effect, especially on the peripheral nervous system [20].

4. Toxicological studies

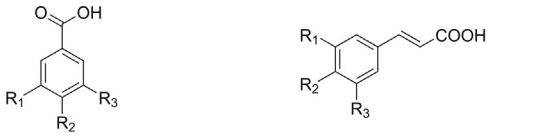
Several plant species are still not the subject of intense scientific research despite their enormous potential as a source of natural substances with potential therapeutic effects. However, some of their components have been identified as being potentially toxic, mutagenic, carcinogenic, and teratogenic [40]. Typically, people tend to believe that the use of plants is safe and devoid of side effects, as they are of natural origin when compared with synthetic substances [41]. However, medicinal plants can be toxic and cause adverse effects or even poisoning [42]. Herbal preparations can become toxic when one of its constituents, which may possess serious toxic effects, remains unidentified or inaccurately identified. Several reports have recorded severe toxicities associated with the use of plant species [40–42]. This observation raises concerns in terms of the potential toxic effects resulting from the short- or long-term use of these plants. Therefore, it is essential to conduct in-depth scientific investigations on the toxicity and risks of plants

prior to any pharmacological and preclinical studies, as it allows better use of these plants while avoiding negative effects on the population's health. Toxicological studies on Moroccan medicinal plants evaluated for their anti-inflammatory and analgesic effects are presented in Table S2 [17,18,21,22,26–28,34,36,38]. The reports of Faridi et al. [27] on *D. staphysagria*, Lachkar et al. [22] on *C. siliqua*, and Hajjaj et al. [26] on *P. rhoeas* have suggested that these plants do not possess any toxic effects, are well tolerated, and exhibit a potent anti-inflammatory effect. In other reports, the evaluation of the in vivo analgesic activities of *T. broussonetii* and *C. ambrosioides* by Elhabazi et al. [35] and Hallal et al. [37], respectively, revealed that these two plants are non-toxic and pose no risk to treated animals.

5. Bioactive compounds of Moroccan medicinal plants with anti-inflammatory and analgesic properties

Medicinal plants contain bioactive molecules that are known as secondary metabolites. These metabolites include phenolic acids, flavonoids, alkaloids, and terpenes. The aqueous, butanol, and ethyl acetate extracts from the leaves and stems of *T. broussonetii* contain several bioactive compounds, including flavonoids, tannins, quinones, saponins, and terpenes [35], with identical chemical classes detected in *C. ambrosioides* leaf extracts [37]. Organic extracts of these medicinal plants are rich in phenolic compounds such as tannins, quinones, and sterols [22]. Table S3 [16,17,21–23,25–27,29,35,37,38] summarizes the identified bioactive compounds and their chemical classes. The identified phenolic acids in Moroccan medicinal plants, with anti-inflammatory and analgesic properties, were gallic, vanillic, syringic, *p*-coumaric, caffeic, ferulic, sinapic, and *p*-hydroxybenzoic acids (Fig. 1). Additionally, Kamal et al. [29] identified these compounds in the vegetable oil of *A. spinosa*. Flavonoids such as epicatechin and quercetin have shown analgesic and anti-inflammatory activities and were identified in *A. spinosa* vegetable oil (Fig. 2) [29].

Moroccan medicinal plants possessing anti-inflammatory and analgesic activities reportedly contain several volatile compounds, including citronellol, 10-*epi*-γ-eudesmol, geraniol, thujone, eucalyptol, santolina triene, bornyl acetate, α-pinene, camphor, *p*-cymene, thymol, carvacrol, linalool, nerol, isopulegol, and citral (Fig. 3). Bounihi et al. [25] identified the volatile compounds in *M. officinalis* leaf essential oil using gas chromatography-mass spectroscopy (GC-MS) analysis; three volatile compounds, namely, nerol, isopulegol, and citral, were identified as the main compounds present in this essential oil. In 2014, Aazza et al. [16] analyzed essential oils isolated from several Moroccan medicinal plants with anti-inflammatory effects such as *F. vulgare*, *C. sempervirens*, *E. globulus*, *C. aurantium*, *C. limon*, and *T. vulgaris*. The results identified numerous compounds, including α-pinene, *p*-cymene, thymol, limonene, linalool, and carvacrol, responsible for the reported anti-inflammatory effects [16]. El Jemli et al. [21] reported that essential oils from *T. articulata* leaves contain bornyl acetate, α-pinene, and camphor as major compounds. In the



1: R_1=R_2=R_3=OH: gallic acid
2: R_1=H, R_2=OH, R_3=OCH_3: vanillic acid
3: R_1=R_3=OCH_3, R_2=OH: syringic acid
4: R_1=R_3=H, R_2=OH: *p*-hydroxybenzoic acid
5: R_1=R_2=OH, R_3=H: caffeic acid
6: R_1=R_3=H, R_2=OH: *p*-coumaric acid
7: R_1=OCH_3, R_2=OH, R_3=H: ferulic acid
8: R_1=R_3=OCH_3, R_2=OH: sinapic acid

Fig. 1. Structures of phenolic acids identified in Moroccan medicinal plants possessing anti-inflammatory and analgesic properties.

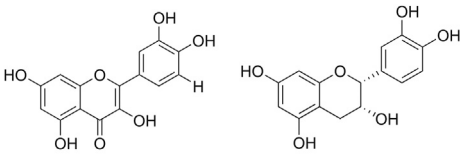


Fig. 2. Structures of flavonoids identified in Moroccan medicinal plants possessing anti-inflammatory and analgesic activities.

available literature, these compounds are known for their anti-inflammatory and analgesic effects. Guaouguaou et al. [38] detected eucalyptol, thujone, and santolina triene as major volatile compounds in *C. cinerea* essential oils. 1,8-Cineole is a monoterpene that demonstrates potent anti-inflammatory and analgesic properties. The essential oils present in *P. graveolens* aerial parts showed anti-inflammatory activity and contained citronellol, 10-*epi*-γ-eudesmol, and geraniol [23].

6. Mechanisms of action of bioactive compounds isolated from Moroccan medicinal plants with anti-inflammatory effects

6.1. Terpenoids

6.1.1. Thymol

Thymol shows an anti-inflammatory effect in both in vitro and in vivo models (Table 3) [43–99]. This compound inhibits certain enzymes involved in the inflammatory reaction, particularly elastase, COX-1, and COX-2 [100,101]. The inhibition of elastase is attributed to the hydrophobic property of thymol [100]. In a proliferation assay, in vivo investigations revealed that thymol suppressed inducible lymphocyte proliferation [102]. In carrageenan-induced paw edema, thymol significantly reduces edema. Furthermore, thymol decreases leukocyte influx into injured areas [103]. In a model using high-fat-diet (HFD)-induced hyperlipidemia and atherosclerosis in rabbits, Yu et al. [50] revealed thymol significantly inhibited proinflammatory cytokines, especially interleukin-1β (IL-1β), IL-6, tumor necrosis factor α (TNF-α), and TNF-β. Additionally, thymol reduced the levels of TNF-α (40%) in doxorubicin (DOX)-induced cardiotoxicity in Swiss albino rats [56]. In another study, thymol decreased the expressions of IL-1β, c-Fos, nuclear factor of activated T-cells (NFAT)-1, and NFAT-2 and significantly inhibited inducible phospho-SAPK/JNK and phospho-STAT3 levels [55]. Recently, thymol was evaluated in a human peritoneal mesothelial cell line (HMRSV5) using a lipopolysaccharide (LPS)-induced inflammatory response [51]. The results revealed a potent suppression of cytokine production, including TNF-α, IL-6, monocyte chemoattractant protein 1 (MCP-1), and α-smooth muscle actin (α-SMA), in a dose-dependent manner. The mechanistic investigation revealed an inhibitory effect of toll-like receptor 4 (TLR4) upregulation, as well as suppression of IKK, IκBα, and p65 phosphorylation [51]. In dextran sulfate sodium (DSS)-induced experimental colitis, thymol reduces the expression of TNF-α, IL-1β, and IL-6 in the mouse colon [54]. Furthermore, thymol demonstrates an inhibitory effect on the LPS-induced secretion of nitric oxide (NO), TNF-α, IL-1β, and IL-6 in macrophages, as well as suppresses NF-κB pathway activation [54]. Thymol is capable of inducing membrane stabilization (84.11%) on assaying human red blood cell membrane stabilization [52].

6.1.2. Carvacrol

Carvacrol (2-methyl-5-[1-methylethyl]-phenol) exhibits several pharmacological activities, including anti-inflammatory effects

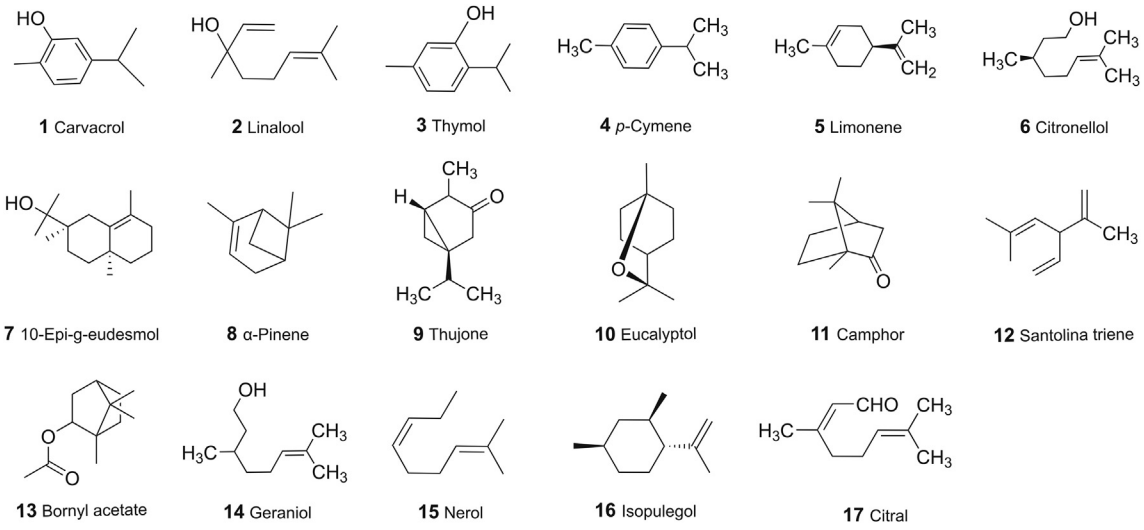


Fig. 3. Structures of terpenoids identified in Moroccan medicinal plants possessing potent anti-inflammatory and analgesic activities.

(Table 3). According to Landa et al. [81], carvacrol inhibits the production of PGE_2 (an inflammatory mediator catalyzed by COX-2). The catalytic activity of COX-2 is also inhibited by carvacrol, and the authors suggested that this compound exhibits a non-selective inhibitory effect on COX-2, reducing PG production by inactivating the arachidonic acid metabolic pathway. In another study, the effect of carvacrol was investigated on transcriptional factors regulating COX-2 expression [104]. Carvacrol inhibits peroxisome proliferator-activated receptors (PPARs), which act as ligand-dependent transcription factors that regulate the transcription of COX-2. In this study, a cell-based transfection assay using bovine arterial endothelial cells was performed. Carvacrol suppresses COX-2 promoter activity by activating PPARα and PPARγ. Furthermore, carvacrol reduces the expression of LPS-induced COX-2 mRNA and protein levels, suggesting that the action of carvacrol on COX-2 is mediated via its agonistic effect on PPARγ [104].

6.1.3. β-Eudesmol

Reportedly, β-eudesmol is a potent anti-inflammatory agent [47–49]. This phenolic monoterpene inhibits the production and expression of IL-6 in phorbol-12-myristate-13-acetate and calcium ionophore A23187-stimulated human mast cells (HMCs) (Table 3). The mechanistic investigation revealed that β-eudesmol suppressed the activation of p38 mitogen-activated protein kinase (MAPK) and NF-κB, as well as caspase-1, and the expression of receptor-interacting protein-2 [49]. In another in vitro and in vivo investigation, Han et al. [47] reported that β-eudesmol suppressed histamine and tryptase in activated HMC-1 cells. Furthermore, β-eudesmol inhibited the expression and activity of histidine decarboxylase, decreased the level of histamine and tryptase released, and reduced the level of intracellular calcium [47]. Kim [48] evaluated the anti-inflammatory effect of β-eudesmol in cell culture (human dermal fibroblasts) and revealed decreased NF-κB activity and reduced IL-1β and TNF-α levels [48].

6.1.4. Limonene

Yoon et al. [105] reported that limonene decreased the production of proinflammatory cytokines and inflammatory mediators in macrophages. This decrease was mediated by the inhibition of LPS-induced NO and PGE_2, which decreased iNOS and COX-2 expression. In another in vitro study, limonene exhibited anti-inflammatory effects by inhibiting specific signaling pathways that result in the inflammatory process in the leukemia HL-60 cell line, including reactive oxygen species (ROS), MCP-1, NF-κB, and p38 MAPK. Limonene suppressed the production of ROS at low concentrations. At higher concentrations, limonene attenuated the expression of p38 MAPK and decreased MCP-1 production [70].

6.1.5. Bornyl acetate

Tung et al. [106] reported that bornyl acetate showed potent anti-inflammatory activity on macrophages. Additionally, bornyl acetate demonstrated significant anti-inflammatory and analgesic effects [107]. It decreased the writhing reaction, pain, and suppressed ear swelling induced by dimethylbenzene, thus clarifying its anti-inflammatory effect. Additional studies have evaluated the impact of bornyl acetate on several immune cells and cytokine secretion [108–110]. Their results revealed that this monoterpene increased the number of $CD4^+$ T lymphocytes, while $CD8^+$ T lymphocytes were not increased. It also suppressed cytokines such as IFN-γ/IL-4 [109].

6.1.6. α-Pinene

α-Pinene exhibits potent activity against the inflammatory process and neuropathic pain [110]. Reportedly, α-pinene exhibits an anti-ischemic activity on neuronal cells by reducing cerebral ischemic injury [111]. This compound prevents neuronal cell death by decreasing ROS generation induced by oxygen-glucose deprivation. Following exposure to T-α-pinene, the expression of proinflammatory cytokines levels in the ischemic brain is reduced, whereas glial cells are hyper-stimulated [111]. In an in vivo model of xylene-induced ear edema using a formalin-inflamed mouse hind paw, Li et al. [45] observed that α-pinene inhibited ear edema at 0.15 h (120%–135% vs. 175%), paw edema at 12 h (146% ± 6%) and decreased COX-2 expression (115% ± 74% vs. 202% ± 20%). More recently, Khoshnazar et al. [44] revealed that α-pinene reduced IL-6 levels in the hippocampus, cortex, and striatum.

6.1.7. 1,8-Cineole

Using the trinitrobenzene sulfonic acid (TNBS)-induced colitis model in rats, Chen et al. [112] showed that 1,8-cineole possessed a crucial anti-inflammatory effect. This activity was related to the capacity of 1,8-cineole to decrease myeloperoxidase (a biomarker of neutrophilic infiltration) [112]. Inhibition of myeloperoxidase

Table 3
Anti-inflammatory effect of volatile compounds identified in Moroccan medicinal plants with anti-inflammatory properties.

Molecules	Experimental approach	Key results	Refs.
α-Pinene	Inhibition of protein denaturation method	IC_{50}=16.40 ± 0.48 μL	[43]
α-Pinene	Focal ischemic stroke in rat induced by transient middle cerebral artery occlusion, followed by 24 h reperfusion	Reduced the levels of IL-6 in the hippocampus, cortex, and striatum	[44]
α-Pinene	Xylene-induced ear edema mouse model Formalin-inflamed mouse hind paw model (Formalin intradermal injection (4%, 20 μL)) Inflammatory infiltrates and cyclooxygenase-2 (COX-2) expression	Inhibited ear edema at 0.15 h (120%–135% vs. 175%) Inhibited hind paw edema at 12 h (146% ± 6%) Suppressed COX-2 (115% ± 4% vs. 202% ± 20%)	[45]
Thujone	Cell culture: Human gingival fibroblasts (HGF-1, ATCC CRL-2014, P 15) WST-1 test Measurement of IL-6 and IL-8 secretion by employing Luminex Xmap magnetic bead technology Uptake experiments of sage infusion constituents in HGF-1 cells	Reduced the release of IL-8 and IL-6 The quantification of compounds detected in the supernatant of Lysed HGF-1 cells showed 0.25 μg of thujone	[46]
β-Eudesmol	Cell culture (HMC-1) Old ICR mice and male 7-week-old Sprague Dawley rats, Histamine assay Western blot analysis HDC assay Tryptase assay Fluorescent measurement of intracellular calcium levels RPMC morphology Enzyme-linked immunosorbent assay (ELISA) PCA reaction	Suppressed histamine and tryptase release Inhibited the expression and activity of histidine decarboxylase in the activated HMC-1 cells Inhibited histamine and tryptase release Decreased intracellular calcium level Decreased the compound 48/80-induced mortality (which induced the degranulation of mast cells as a basic secretagogue) and the ear-swelling response Suppressed the serum levels of histamine, IgE, IL-1β, IL-4, IL-5, IL-6, and IL-13	[47]
β-Eudesmol	Cell culture [human dermal fibroblasts (HDF)] WST-1 assay NF-κB luciferase assay	Decreased NF-κB activity Decreased interleukin-1β (IL-1β) Decreased tumor necrosis factor-alpha (TNF-α)	[48]
β-Eudesmol	Cell culture (HMC-1) MTT assay Assay of IL-6 production RNA isolation and RT-PCR Western blot analysis Caspase-1 activity Transient transfection and luciferase assay	Inhibited the production and expression of IL-6 on phorbol 12-myristate 13-acetate and calcium ionophore A23187-stimulated human mast cells (HMCs) Suppressed the activation of p38 mitogen-activated protein kinase (MAPK) and NF-κB Suppressed the activation of caspase-1 and expression of receptor-interacting protein-2	[49]
Thymol	High fat diet-induced hyperlipidemia and atherosclerosis in rabbits Cytokines IL-1β, IL-6, TNF-α, and TNF-β	Decreased proinflammatory cytokines IL-1β, IL-6, TNF-α, and TNF-β when compared with the high-cholesterol diet group (HC)	[50]
Thymol	Cell culture [human peritoneal mesothelial cell line (HMRSV5)] Lipopolysaccharide (LPS)-induced inflammatory response WST-8 cell proliferation and cytotoxicity assay kit Rhoa pull-down assay Western blot analysis Immunofluorescence ELISA	Inhibited the production of cytokines TNF-α, IL-6, monocyte chemoattractant protein 1 (MCP-1), and α-smooth muscle actin (α-SMA) in a dose-dependent manner Inhibited the upregulation of TLR4 and the phosphorylation of IKK, IκBα, and p65	[51]
Thymol	HRBC (human red blood cell) membrane stabilization method	Percent membrane stabilization = 84.11%	[52]
Thymol	Cutaneous acute inflammation model induced by croton oil in mice Anthralin induced ear edema model Imiquimod induced psoriasis-like inflammation model	Gel containing thymol encapsulated in nanostructured lipid carriers (NLC) exhibited better anti-inflammatory activity than free thymol	[53]
Thymol	Dextran sulfate sodium (DSS)-induced experimental colitis in mice Cell culture (RAW 264.7 cells) MTT assay Proinflammatory cytokines (TNF-α, IL-1β, and IL-6) Nuclear factor-κB (NF-κB) PCR ELISA Western blot	Reduced mRNA expressions of TNF-α, IL-1β, and IL-6 in the colon Inhibited LPS-induced secretion of nitric oxide, TNF-α, IL-1β, and IL-6 in macrophages Suppressed the activation of the NF-κB pathway	[54]
Thymol	Cell culture (a murine macrophage cell line J774.1) LPS-stimulated J774.1 mouse macrophages MTT reduction assay Real time-PCR Cytokine measurements Transcription factor assessments Cytoplasmic and nuclear protein extraction Western blot analyses	Reduced IL-1β expression from 2.40 ± 0.24 to 1.12 ± 0.08 Decreased the expression of c-Fos, NFAT-1, and NFAT-2 Decreased inducible levels of phospho-SAPK/JNK and phospho-STAT3 and reduced phospho-IκBα	[55]
Thymol	Doxorubicin (DOX)-induced cardiotoxicity in Swiss albino rats Measurement of TNF-α by ELISA	Reduced TNF-α level (40%)	[56]
Bornyl acetate	Human chondrocytes Real-time PCR Measurement of cytokine levels by ELISA Western Blot Analysis	Elevated IL-11 expression at mRNA and protein levels Elevated the expression of AP-1 component c-FOS at mRNA and protein levels Inhibited the expression of matrix metalloproteinase (MMP)-1 and MMP-13 in OA chondrocytes Elevated the expression of IL-11 through activating the AP-1 transcriptional activity Upregulated IL-11 in human primary chondrocytes	[57]

(*continued on next page*)

Table 3 (*continued*)

Molecules	Experimental approach	Key results	Refs.
Bornyl acetate	Lipopolysaccharide-induced acute lung injury murine model Cell culture: RAW 264.7 cells MTT assay Measurement of TNF-α, IL-1β, and IL-6 by ELISA	Downregulated the levels of proinflammatory cytokines Reduced the number of total cells, neutrophils, and macrophages in bronchoalveolar lavage fluid (BALF) Attenuated the histologic alterations in the lung Decreased the wet-to-dry weight ratio in BALF Suppressed NF-κB inhibitor alpha, extracellular regulated protein kinases, c-*Jun* N-terminal kinase, and p38 mitogen-activated protein kinase activation	[58]
Citronellol	Carrageenan-induced pleurisy 25, 50, and 100 mg/kg Quantification of TNF-α Evaluation of leukocytes	Inhibited both neutrophil infiltration and increased TNF-α levels in the exudates from carrageenan-induced pleurisy Decreased nitric oxide production by LPS-stimulated macrophage	[59]
Citronellol	7,12-Dimethylbenz(*a*)anthracene (DMBA)-induced mammary carcinogenesis in rats Citronellol at dose of 50 mg/kg body weight Immunohistochemical study Reverse transcription polymerase chain reaction analysis Western blot protein expression analysis	Down-regulated NF-κB expression Increased IL-10 level in mammary tissues Decreased IL-6, TNF-α, and COX-2 levels	[60]
p-Cymene	LPS-induced acute lung injury Measurement of TNF-α, IL-1β, and IL-6 by ELISA Pulmonary myeloperoxidase activity Western blot analysis	Reduced the proinflammatory cytokines (TNF-α, IL-1β, and IL-6) Reduced lung water gain, inflammatory cell infiltration, and lung tissue myeloperoxidase activity Blocked the phosphorylation of IκBα protein and activation of the mitogen-activated protein kinase signaling pathway Decreased focal thickening, congestion, pulmonary edema, and inflammatory cell infiltration	[61]
p-Cymene	Paw edema in mice model induced by 1% carrageenan 20 or 40 mg/kg	Inhibited the development of carrageenin-induced paw edema (1%)	[62]
p-Cymene	Leukocyte migration induced by carrageenan 25, 50, and 100 mg/kg	Decreased leukocyte migration at all doses tested	[63]
Citral	Cell culture: RAW 264.7 cell line	Inhibition NO production=84%	[64]
Citral	LPS-induced inflammation in human umbilical vein endothelial cells (HUVECs) Measurement of TNF-α and IL-8 using ELISA Western blotting: vascular cell adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1), NF-κB, and peroxisome proliferator-activated receptor-γ (PPAR-γ)	Decreased the levels of WBCs and inflammatory cytokines (TNF-α and IL-6) Inhibited LP-induced myeloperoxidase (MPO) Suppressed VCAM-1 and ICAM-1 expression Inhibited LPS-induced NF-κB activation in HUVECs Activated PPAR-γ	[65]
Citral	Air pouch model Leukocyte count Measurement of cytokines IL-1β, TNF-α, and IL-6 by ELISA RT-qPCR	Decreased TNF-α, IL-1β, and IL-6	[66]
Citral	Carrageenan-induced paw edema test Leukocyte migration into the peritoneal cavity 100 and 200 mg/kg	Reduced carrageenan-induced paw edema Reduced the leukocyte migration	[67]
Citral	Carrageenan-induced pleurisy J774 macrophages cell line Determination of TNF-α Cell viability assay	Reduced total leukocytes and TNF-α level The complexation efficiency of CIT/β-CD and CIT/HP-β-CD were 78.6% and 71.7%, respectively Cell viability in macrophages	[68]
Limonene	Cell cultures: Human chondrocytic cell line, C28/I2 NF-κB—DNA binding activity Nitric oxide production Western blot analysis NF-κB transcription factor assay qRT-PCR	Inhibited IL-1-induced NO production Reduced IL-1β-induced IκBα phosphorylation and degradation as well as NF-κB—DNA binding Reduced p38 phosphorylation Increased phosphorylated ERK1/2 Reduced MMP-1 and -13 levels by 51% and 39%, respectively	[69]
Limonene	Eotaxin-stimulated HL-60 clone 15 cells Measurement the level of reactive oxygen species (ROS), MCP-1, NF-κB, and p38 MAPK Chemotaxis assay NF-κB—DNA binding assay ELISA Immunoblot analysis	Inhibited ROS production Reduced MCP-1 production Inhibited cell chemotaxis in a p38 MAPK dependent manner Inactivated eosinophil migration Attenuated NF-κB activity in DF-HL-60 clone 15 cells	[70]
Limonene	Ethanol-induced gastric ulcers 25, 50 or 100 mg/kg Measurement of TNF-α, IL-6, IL-1β, and IL-10 by ELISA Measurement of myeloperoxidase (MPO) activity	Reduced MPO activity Decreased the levels of TNF-α, IL-6, and IL-1β Increased IL-10 level Downregulated the expression of NF-κB, IL-1β, MPO, and IL-10 Upregulated glutathione peroxidase expression	[71]
Limonene	TNBS (2,5,6-trinitrobenzene sulfonic acid)-induced colitis NF-κB activity assessment Human colon carcinoma cell line HT-29/B6 Measurement of TNF-α 10 mg/kg	Significantly reduced intestinal inflammatory scores Significantly lowered TNF-α serum concentrations Inhibited TNF-α-induced NF-κB translocation in fibroblast cultures	[72]

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Table 3 (*continued*)

Molecules	Experimental approach	Key results	Refs.
Limonene	TPA-induced-mouse skin edema 50 and 100 mg/kg	Significantly reduced the TPA-induced (a) edema Reduced the expression of cyclooxygenase 2, ornithine decarboxylase activity, and [3H] thymidine incorporation into DNA Restored the level of reduced glutathione, glutathione peroxidase, glutathione reductase, glutathione S-transferase, catalase, and malondialdehyde production	[73]
Geraniol	Fructose-fed rats Western blot studies PCR studies Assessment of multidrug resistance-associated protein 2 (MRP2) activity Assessment of interleukins	Increased the protein and mRNA expression of MRP2 Improved the intestinal redox unbalance Restored IL-1β levels and partially IL-6 levels	[74]
Geraniol	Imiquimod-induced psoriasis-like animal model Cell culture: Human embryonic kidney 293T cells (HEK293T) Cell viability: MTS assay kit Measurement of cytokines Western blotting	Inhibited the KV1.3 ion channel Reversibly blocked KV1.3 currents IC_{50} of 490.50 ± 1.04 μM at +40 mV in HEK293T cells Inhibited cytokine secretion of activated human T cells: IL-2, TNF-α, and IFN-γ Reduced psoriasis area and severity index scores Ameliorated the deteriorating histopathology Decreased the degree of splenomegaly	[75]
Geraniol	Assessed in traumatic spinal cord injury (SCI) Assessing locomotor recovery: Basso, Beattie, and Bresnahan (BBB) test ELISA Western blot analysis	Significantly increased BBB scores Significantly inhibited the spinal cord water content in SCI rats Significantly decreased TNF-α, IL-1β, and IL-6 Significantly suppressed NF-κB protein expression	[76]
Geraniol	7,12-Dimethylbenz[*a*]anthracene (DMBA)-induced hamster buccal pouch carcinogenesis 250 mg/kg Real-time PCR analysis	Significantly restored the expression of p53, Bcl-2, Bax, proliferating cell nuclear antigen (PCNA), and vascular endothelial growth factor Significantly decreased COX-2 and c-FOS Suppressed the expression of cyclin D1 and NF-κB	[77]
Geraniol	Peripheral blood mononuclear cells (PBMCs) Cell viability: 3-(4,5-Dimethyl-thiazol-2-yl)-2,5-diphenyltetrazolium bromide colorimetric assay ELISA	Increased IL-10 production by human monocytes No effect on TNF-α production	[78]
Geraniol	Atherogenic diet induced fibrosis in experimental hamsters 100 mg/kg Immunohistochemical analysis	Downregulated NF-κB expression Significantly prevented the depletion of antioxidants and preserved the tissue damage induced by oxidative stress	[79]
Carvacrol	Complete Freund's adjuvant (CFA)-induced paw inflammation in mice 50 and 100 mg/kg Measurement of prostaglandin E_2 (PGE_2) by enzyme immunoassay ELISA Real-time PCR	Attenuated the paw edema Reduced the IL-1β and PGE_2 levels Reduced the COX-2 and IL-1β mRNA expression Enhanced the levels of IL-10 and the IL-10 mRNA expression in the inflamed paw	[80]
Carvacrol	COX-2 assay	Inhibited the production of PGE_2 catalyzed by COX-2 (IC_{50}=0.8 μM) Inhibited COX-2 (IC_{50}=0.7 μM)	[81]
Carvacrol	Veterans exposed to sulfur mustard (SM) Twenty-one patients 1.2 mg/kg/day Measurement of TNF-α and MCP-1	Decreased TNF-α levels Decreased MCP-1	[82]
Carvacrol	Cisplatin-induced nephrotoxicity 15 mg/kg Measurement of TNF-α levels	Reduced TNF-α levels	[56]
Carvacrol	Cell Culture: Human Neuroblastoma SH-SY5Y cell line Hydrogen Peroxide Cell viability using MTT assay	Downregulated the transcription factor NF-κB	[83]
Carvacrol	Carcinogenicity in the Colon of Fischer 344 rats 50 mg/kg Immunohistochemical analysis of inducible nitric oxide synthase (iNOS) and IL-1β	Significantly decreased MPO levels Significantly decreased the levels of the tissue and serum nitrite Decreased the number of positive cells for IL-1β and iNOS expression	[84]
Camphor	Male Wistar albino rats 1000, 2000, and 4000 mg/kg Hepatic and pulmonary proinflammatory cytokines and chemokines ELISA Liver and lung immunohistochemistry	Significantly increased the levels of TNF-α, IL-1β, and IL-6 in liver and lung at doses of 2000 and 4000 mg/kg Significantly increased IL-10 at doses of 1000 and 4000 mg/kg Significantly increased the expressions of NF-κB, COX-2, RANTES, and MCP-1	[85]
Camphor	Neutrophil chemotaxis, croton oil induced-ear edema MPO activity Phagocytic activity of macrophages in Swiss mice 0.5, 1, 2.5, and 5 mg/ear 100, 200, or 400 mg/kg	Reduction on leukocyte migration toward N-formyl methionyl leucyl phenylalanine (fMLP) Reduced leukocyte migration toward N-formyl methionyl leucyl phenylalanine (fMLP) No significant reduction in ear edema or MPO activity at any of the doses tested Significantly reduced ear edema and MPO activity No effect on the phagocytic activity of macrophages	[86]
Camphor	Male Wistar albino rats 1000, 2000, and 4000 mg/kg Renal and testicular proinflammatory chemokines and cytokines	Significantly increased the levels of TNF-α, IL-1β, and IL-6 in kidney and testes at doses of 2000 and 4000 mg/kg Significantly increased IL-10 by 1000 mg/kg body weight in both tissues Significantly increased the expressions of renal and testicular NF-κB, COX-2, RANTES, and MCP-1	[87]

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Table 3 (*continued*)

Molecules	Experimental approach	Key results	Refs.
Camphor	Turpentine induced inflammation model	Significantly reduced paw volume in animals	[88]
Linalool	Cigarette smoke (CS)-induced pulmonary inflammation in mice Measurement of the numbers of macrophages and neutrophils in BALF ELISA Western blotting	Inhibited the infiltration of inflammatory cells Inhibited TNF-α, IL-6, IL-1β, IL-8, and MCP-1 production Inhibited CS-induced lung MPO activity and pathological changes Suppressed CS-induced NF-κB activation in a dose-dependent manner	[89]
Linalool	Xylene-induced ear edema mouse model Formalin-inflamed mouse hind paw model Formalin intradermal injection (4%, 20 μL) Inflammatory infiltrates and cyclooxygenase-2 expression	Inhibited ear edema at 0.15 h (120%–135% vs. 175%) Inhibited hind paw edema at 12 h (136% ± 3%) Decreased COX-2 (116% ± 4% vs. 202% ± 20%)	[90]
Linalool	Endotoxin-induced inflammatory effect in mice Measurement of IL-1β, IL-18, TNF-α, IFN-γ, and HMGB-1 by ELISA Analysis of IL-1β, TNF-α, and IFN-γ in spleen and mesenteric lymph nodes (MLNs) by ELISA Determination of NF-κB Western blot analysis Caspase-1 activity assay 2.6 and 5.2 mg/kg	Significantly prevented nitrate/nitrite Suppressed the elevation of IL-1β, IL-18, TNF-α, and IFN-γ in peripheral blood Prevented endotoxin-induced elevation of proinflammatory parameters in spleen and MLNs Prevented endotoxin-induced NF-κB activation in spleen and MLNs Prevented caspase-1 activation	[91]
Linalool	Ovalbumin-induced pulmonary inflammation Measurement of IL-4, IL-5, IL-13, and immunoglobulin E (IgE) production by ELISA Western blot analysis Cell culture: H292 airway epithelial cells	Significantly inhibited the level of eosinophil, Th2 cytokines, and IgE Decreased levels of iNOS expression and protein kinase B (AKT) activation in lung tissue Downregulated the activation of MAPK and NF-κB Attenuated MCP-1 in LPS-stimulated H292 airway epithelial cells	[92]
Linalool	LPS-stimulated RAW 264.7 macrophages Lipopolysaccharide-induced lung injury model Enzyme-linked immunosorbent assay Western blotting	Attenuated the production of LPS-induced TNF-α and IL-6 Blocked phosphorylation of IkB-α protein, p38, c-Jun terminal kinase, and extracellular signal-regulated kinase	[93]
Linalool	Streptozotocin-induced diabetic rats 25 mg/kg Analysis of transforming growth factor (TGF)-β1, NF-κB p65, and nephrin	Decreased the expression of TGF-β1 and NF-κB Reduced 3-NT and 2, 4-DNP immunoreactivity Modulated podocyte foot process changes Reduced the thickening of basement membrane Prevented podocyte loss and maintained the slit pore integrity Upregulated the expression of nephrin in the kidney of diabetic rats	[94]
Linalool	CFA-induced persistent inflammation 50 or 200 mg/kg Measurement of paw edema using a plethysmometer Administration of inflammatory mediators	Reduced CFA-induced paw edema Inhibited the biting response induced by IL-1β and TNF-α	[95]
Eucalyptol	Healthy volunteers Cell cultures: Fetal calf serum (FCS)-stimulated human monocytes	Strongly inhibited O_2^- (−53%) Inhibited superoxide dismutase (SOD; −28%) Inhibited H_2O_2 (−48%) Increased total cellular antioxidant activity Significantly inhibited TNF-α	[96]
Eucalyptol	Patients with severe bronchial asthma Eucalyptol at dose 200 mg, 1.8-cineol t.i.d for 12 weeks	Decreased oral steroids	[97]
Eucalyptol	CS-induced acute pulmonary inflammation in mice Inhalation of 1, 3, and 10 mg/mL Measurement of inflammatory markers by ELISA Western blotting	Reduced total leukocyte numbers compared with the CS group Reduced macrophage numbers Reduced MPO Reduced cytokine levels (IL-1β, IL-6, and KC) Decreased NF-κB and p65 Reduced ROS, SOD, catalase (CAT), and malondialdehyde Attenuated CS-induced histopathological alterations	[98]
Eucalyptol	Copper-exposed common carp	Significantly increased SOD, glutathione peroxidase, and CAT activity in fish serum Decreased MDA in fish serum Significantly upregulated SOD and CAT in fish kidney Downregulated TNF-α, IL1β, and IL8 gene expression in fish kidney	[99]

production indicates that this compound could play an important role in preventing gastrointestinal inflammation and ulceration [113].

6.1.8. Geraniol

The anti-inflammatory activity of geraniol has been previously investigated [114]. This bioactive compound exhibits a dose-dependent, anti-inflammatory effect on lymphocyte proliferation in vitro. An in vivo study using a cardiac allograft model showed that geraniol prolonged graft survival [114]. Mevalonate kinase deficiency is reportedly responsible for the recruitment of inflammatory cells. The inhibition of the mevalonate pathway can reduce intermediate metabolites such as geranylgeranyl-pyrophosphate (GGPP), which is responsible for IL-1β production in monocytes. Both in vitro and in vivo, geraniol is able to reduce the levels of inflammatory markers. Therefore, this molecule can provide a crucial alternative to treat inflammation associated with mevalonate kinase deficiency [115].

6.1.9. Linalool

Linalool is another monoterpene known to exhibit anti-inflammatory effects. This compound exhibits a significant effect on chronic inflammatory hypersensitivity induced by complete Freund's adjuvant. In adult female Swiss mice, an i.p. injection of linalool at 50 and 200 mg/kg reduces hypersensitivity and paw edema [95]. Linalool also shows anti-inflammatory activity in the carrageenan-induced edema model in rats [116].

6.1.10. Nerol and citral

Using an animal model, González-Ramírez et al. [117] revealed

that nerol exhibited anti-inflammatory and antinociceptive (30–300 mg/kg p.o.) effects. Nerol suppressed several pathological alterations induced by oxazolone (OXA)-induced colitis. These effects were associated with the inhibited expressions of several inflammatory mediators, such as IL-13 and TNF-α. Citral exhibits potent anti-inflammatory effects by activating peripheral neutrophils and inducing their adherence [118].

6.2. Phenolic acids

6.2.1. Gallic acid

Gallic acid is a crucial phenolic compound present in several Moroccan medicinal plants with anti-inflammatory effects [119,120]. Numerous in vitro investigations were undertaken to assess the anti-inflammatory effects of gallic acid using cellular models (Table 4) [47,119–152].

Using the LPS-stimulated murine macrophage cell line (RAW 264.7), gallic acid inhibited PGE_2, with no effects on IL-6 and TNF-α production [121]. By employing the same cellular model, gallic acid revealed a potent anti-inflammatory impact by suppressing NO, PGE_2, and IL-6 expression in LPS-induced RAW 264.7 cells [125]. Additionally, gallic acid shows a potent anti-inflammatory effect in animal models. This compound reportedly decreased the production of PGE_2 and calcitonin in testicular tissues of young rats [126]. Furthermore, gallic acid significantly reduces the proinflammatory cytokine IL-6 and chemokines CCL7 and CXCL8 in an in vivo model of OXA-induced dermatitis [124]. This compound reduces the inflammatory response related to oxidative stress in obese C57BL/6J mice fed an HFD [120]. The results revealed that gallic acid regulated dyslipidemia, fasting hyperglycemia, and the expression levels of TNF-α, PPAR-γ, IL-6, and transcriptional factor NF-κB [120]. Wei et al. [119] observed similar results in an in vivo model of intra-abdominal adhesions. Gallic acid suppresses inflammation owing to its capacity to inhibit the formation of intra-abdominal adhesions in a rat model, reduces IL-6, TNF-α, and TGF-β expression, and represses the phosphorylation of transcriptional factor NF-κB [119].

6.2.2. Caffeic acid

Caffeic acid is a phenolic acid primarily found in various Moroccan medicinal plants with anti-inflammatory effects (Table 4). In an in vivo investigation using animal models, this compound exhibits a marked anti-inflammatory effect, as demonstrated by various bioassays [146,147,149–151]. In the carrageenan-induced edema model, caffeic acid inhibits NO and PGE_2 production [148]. It also decreases TNF-α, iNOS, and COX-2 expressions by downregulating transcriptional NF-κB [148]. In another in vitro study using LPS-induced NO production in RAW 264.7 macrophages, caffeic acid inhibits LPS-induced iNOS expression in RAW 264.7 macrophages and inhibits carrageenan-induced paw edema [149]. Recently, Schröter et al. [150] revealed that caffeic acid induced a significant decrease in iNOS, TNF-α, and IL-6 expression. This action is associated with a decline in the translocation of NF-κB/rel-like containing protein 65 into the nucleus [150].

6.2.3. Ferulic acid

Ferulic acid reveals an anti-inflammatory effect in various in vitro and in vivo studies (Table 4). This compound presents potent anti-inflammatory activity (in vitro) in rat vascular smooth muscle cells (VSMCs) [145]. Ferulic acid decreases IL-6, IL-1β, and TNF-α levels and inhibits iNOS gene expression in H_2O_2-induced VSMCs, as well as H_2O_2-induced iNOS mRNA expression. This inhibition involves a decrease in p22phox, p47phox, and gp91phox mRNA expression, with reduced gp91phox, p47phox, and NOX4 levels in H_2O_2-induced VSMCs [145]. Doss et al. [143] evaluated the anti-inflammatory activity of ferulic acid against monosodium urate crystal-induced inflammation in rats. The results revealed a decrease in paw edema, with levels of articular elastase and lysosomal enzymes significantly reduced. More importantly, ferulic acid suppresses TNF-α, IL-1β, NLRP3, and caspase-1 expressions by inhibiting the transcriptional factor NF-κB p65. In another experimental model, mice were exposed to unpredictable chronic mild stress, and this molecule decreased several neuro-inflammatory factors such as IL-1β and TNF-α in the prefrontal cortex [142].

6.2.4. Sinapic acid

In an in vitro study using the BEAS-2B cell line, sinapic acid inhibits NF-κB activation and decreases IL-6 and IL-8 expression [138]. Furthermore, this acid decreases TNF-α in TNBS-induced colonic inflammation in mice [139]. In an in vitro cellular model employing rat chondrocytes, sinapic acid revealed an anti-inflammatory effect mediated via MAPK pathway with inhibiting IL-1β-induced NO, and PGE_2 expression, and a decrease in iNOS and COX-2 production [140]. In an animal model of gentamicin-induced nephrotoxicity, sinapic acid inhibited gentamicin-induced expression of TNF-α and IL-6, while suppressing the expression of NF-κB and NF-κB-DNA binding activity [141].

6.3. Flavonoids

6.3.1. Quercetin

Several reports have evaluated the anti-inflammatory properties of quercetin [153,154]. Both COX-1 and 12-LOX are involved in mediating the inflammatory response. Inhibiting these enzymes or reducing their activities is a crucial step in suppressing inflammation. Lesjak et al. [155] revealed that quercetin inhibited the activity of both enzymes in a dose-dependent manner. The expression of these enzymes is often associated with an increase of TNF-α. Quercetin reduced TNF-α expression in a mouse model of endotoxemia [156]. In a cellular model, this flavonoid inhibits the expression of several inflammatory mediators, including NO, IL-6, MCP-1, IP-10, regulated upon activation, normal T cell expressed, and secreted (RANTES), granulocyte/macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), TNF-α, leukemia inhibitory factor (LIF), lipopoly saccharide-induced CXC chemokine (LIX), and vascular endothelial growth factor (VEGF). This inhibition is mediated by the repression of signal transducer and activator of transcription 1 (STAT1) and STAT3, which regulates the transcriptional activity of these mediators [154]. In an in vivo investigation, quercetin suppresses inflammation in mice [153]. Additionally, it decreases skin inflammation by reducing irritation, edema, and leukocyte accumulation. In mice, quercetin triggers tissue regeneration by stimulating new tighter collagen fibers in tetradecanoylphorbol acetate (TPA)-induced skin inflammation [153]. Moreover, in HFD-induced adipose tissue macrophage infiltration and inflammation in mice, quercetin suppresses the levels of proinflammatory cytokines TNF-α, IL-6, and MCP-1 in the epicardial adipose tissue, enhancing AMPK1 and SIRT1 activity in adipose tissues. Quercetin regulates bone marrow-derived macrophage polarization and inflammation through the AMPK1/SIRT1 pathway [157]. In another experimental model using rat adjuvant arthritis, quercetin reduces IL-1β, c-reactive protein (CRP), and MCP-1 levels [158]. These effects are associated with its potential to restore plasma antioxidant capacity. Molecular analysis of the anti-inflammatory effect revealed that quercetin inhibited the enzymatic activity of proinflammatory 12/15-LOX in lung and liver tissues, as well as their expression. These actions are associated with a decrease in transcriptional factor NF-κB activity [158].

Table 4
Anti-inflammatory effect of phenolic compounds identified in Moroccan medicinal plants with anti-inflammatory properties.

Molecules	Experimental approach	Key results	Refs.
Gallic acid	Intra-abdominal adhesions in a rat model Measurement of interleukin (IL)-6, tumor necrosis factor (TNF)-α, and transforming growth factor (TGF)-β by ELISA Detection of NF-κB phosphorylation by western blotting Immunohistochemistry performed using the SABC kit	Inhibited the formation of intra-abdominal adhesions in a rat model Significantly reduced IL-6, TNF-α, and TGF-β serum levels Significantly reduced NF-κB phosphorylation	[119]
Gallic acid	Cell culture: murine macrophage cell line RAW 264.7 Cell Counting Kit-8 (CCK-8) assay Measurement of TNF-α, IL-6, and prostaglandin E2 (PGE_2)	Inhibited PGE_2 production in lipopolyssacharide (LPS)-stimulated RAW 264.7 macrophages No effect on IL-6 production No effect on TNF-α production	[121]
Gallic acid	Porcine coronary restenosis model Histopathologic analysis Evaluation of arterial injury score Inflammation scores and fibrin scores	Suppressed vascular inflammation in stented arteries Inflammation score was significantly lower in the two groups with gallic acid [gallic acid-eluting stents (GES) and gallic acid and sirolimus-eluting stents (GSES)]	[122]
Gallic acid	Fluoxetine-induced liver damage Measurement of TNF-α with ELISA	Reduced TNF-α	[123]
Gallic acid	Oxazolone-induced dermatitis-like mice model Histological examination Eosinophils culture and co-culture of eosinophils and dermal fibroblasts Measurement of cytokines/chemokines	No significant suppression of IL-31- and IL-33-stimulated eosinophils Significantly reduced the proinflammatory cytokine IL-6 and chemokines CCL7 and CXCL8	[124]
Gallic acid	Cell culture (RAW 264.7 cells) Cell viability assay (cellTiter 96® nonradioactive cell proliferation assay kit) Measurement of IL-6, PGE_2, COX-2, and nitrite production Griess reagent Immunoassay kit ELISA Western blotting	Suppressed the levels of nitric oxide (NO), PGE_2, and IL-6 production in LPS-induced RAW 264.7 cells	[125]
Gallic acid	Microwave radiation (2.45 GHz) inducted inflammatory in testicular young rats Histopathological analyses Immunohistochemical examination	Decreased PGE_2 and calcitonin gene related peptide (CGRP) staining in tubules of the testes	[126]
Gallic acid	High fat diet (HFD)-fed male C57BL/6J mice Inflammation and oxidative stress in an obese state	Regulation of dyslipidemia, fasting hyperglycemia, and expression of TNF-α, Peroxisome proliferator-activated receptor gamma (PPAR-γ), IL-6, and the transcriptional factor NF-κB involved in complications associated with diabetes and obesity	[120]
P-coumaric acid	LPS-stimulated RAW 264.7 cells Western blot analysis	Significantly inhibited cyclooxygenase (COX)-2, inducible nitric oxide synthase (iNOS), TNF-α, and IL-1β mRNA expression in LPS-stimulated RAW 264.7 macrophages Suppressed COX-2 and iNOS protein expression Suppressed the LPS-induced NF-κB pathway Suppressed the LPS-induced mitogen-activated protein kinase (MAPK) pathway	[127]
P-coumaric acid	LPS-induced inflammatory changes in rats Western blotting	Reduced inflammatory cytokines (COX-2 and TNF-α)	[128]
P-coumaric acid	Cell culture (RAW 264.7 macrophage cell line) LPS-stimulated RAW 264.7 macrophage cells Cell viability: Methylthiazolyldiphenyl-tetrazolium bromide (MTT) method Measurement of NF-κB activity	Inhibited NF-κB activation by 15%	[128]
P-coumaric acid	LPS-induced cardiac inflammation Measurement of IL-1β and IL-18 level by ELISA	Significantly suppressed IL-18 and IL-1β levels in heart tissue Significantly reduced IL-1β and myeloperoxidase (MPO) levels in bronchoalveolar lavage fluid Modulated activation of MiR-146 in LPS-induced cardiac injury	[129]
P-coumaric acid	Collagen-induced arthritis (CIA) model rats Measurement of TNF-α and IL-6 levels by ELISA	Decreased the arthritis index Decreased TNF-α and IL-6 levels	[130]
P-coumaric acid	Cell line (A549 human lung adenocarcinoma cell line) Inflammatory process induced by cigarette smoke extract (CSE) in epithelial cells Cell viability assay Measurement of IL-8 levels using ELISA	Significantly reduced IL-8 production by 24%, 55%, and 74% at 10, 20, and 100 μm, respectively EC_{50}=15.2 ± 1.3 μM	[131]
Syringic acid	HFD-induced obese mice Measurement of cytokine and chemokine levels	Significantly lowered the levels of proinflammatory markers, serum TNF-α, IFN-γ, IL-6, and MCP-1 Significantly downregulated expression of inflammatory genes, such Tlr4, Myd88, NF-κB, TNF-α, and IL-6 in the liver Suppressed long-term HFD-induced inflammation through inhibition of the TLR4 pathway	[47]
Vanillic acid	HFD-fed rats Evaluated COX-2 and MCP-1 Western blot analysis	Significantly down-regulated hepatic inflammation-related Proteins (COX-2 and MCP-1)	[132]
Vanillic acid	Animal model of transient bilateral common carotid artery occlusion and reperfusion (BCCAO/R) Measurement of IL-6, TNF-α, and IL-10 cytokines ELISA	Significantly restored the spatial memory Decreased levels of IL-6, TNF-α, and TUNEL positive cells Increased IL-10 levels in hippocampi of BCCAO/R rats	[133]
Vanillic acid	Human mast cell line (HMC-1) phorbol-12-myristate 13-acetate plus calcium ionophore A23187 (PMACI) -stimulation	Decreased levels of thymic stromal lymphopoietin and pro-inflammatory cytokines in HMC-1 cells Inhibited activities of caspase-1 and NF-κB (p65) Suppressed phosphorylation of MAPKs in PMACI treated HMC-1 cells	[134]

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Table 4 (*continued*)

Molecules	Experimental approach	Key results	Refs.
Vanillic acid	LPS-induced inflammatory responses in mouse peritoneal macrophages MTT assay ELISA Western blot analysis Caspase colorimetric assay kit Immunoassay kits	Inhibited LPS-induced production of TNF-α and IL-6 Suppressed the enhanced COX-2 levels and PGE_2 and NO production Suppressed the activation of NF-κB and caspase-1 Inhibited PGE_2 production=30.3% ± 9.09% Inhibited the production of TNF-α (61.38% ± 3.81%) and IL-6 (38.62% ± 2.63%) Inhibited nitric oxide production (18.1% ± 2.56%)	[135]
Vanillic acid	Murine models of inflammatory pain Writhing response tests Formalin test Carrageenan- and Complete Freund's adjuvant (CFA)-induced mechanical hyperalgesia Carrageenan- and CFA-induced paw edema Measurement of cytokine by ELISA NF-κB activity	Inhibited acetic acid- and phenyl-benzoquinone (PBQ)-induced writhing response Inhibited formalin- and CFA-induced paw flinch and time spent licking the paw Inhibited carrageenan-induced mechanical hyperalgesia, paw edema, and neutrophil and macrophage recruitment Inhibited CFA-induced mechanical hyperalgesia, paw edema, and neutrophil and macrophage recruitment Prevented carrageenan-induced oxidative stress Inhibited carrageenan-induced proinflammatory cytokines (IL-1β, TNF-α, and IL-33) production Suppressed carrageenan-induced activation of NF-κB	[136]
Vanillic acid	Ovalbumin (OVA)-induced asthma in rat model Orally administered at doses of 25 and 50 mg/kg Histopathological analysis Analyzed the levels of serum IgE, inflammatory cytokines TNF-α, IFN-γ, IL-4, IL-5, and IL-13 by ELISA	Reduced the infiltration of the inflammatory cells Significantly reduced levels of inflammatory cytokines TNF-α, IL-4, IL-5, and IL-13, and significantly increased the level of IFN-γ Elevated the levels of glutathione, superoxide dismutase, and catalase, and reduced the levels of malondialdehyde (MDA), reactive oxygen species (ROS), and IgE	[137]
Sinapic acid	Cell culture: BEAS-2B cells Luciferase reporter assay Measurements of IL-6 and IL-8 by ELISA Target sinapic acid derivatives	The targeted compound inhibited NF-κB activation and decreased IL-6 and IL-8 expression in BEAS-2B cells	[138]
Sinapic acid	2,4,6-Trinitrobenzenesulfonic acid (TNBS)-induced colitis in mice Macroscopic assessment of colitis severity Microscopic assessment of colitis severity MPO activity Measurement of TNF-α level by ELISA	Significantly decreased TNF-α in TNBS-induced colonic inflammation Reduced MPO activity	[139]
Sinapic acid	Rat chondrocytes Cell viability assay: CCK-8 assay Measurement of NO and PGE_2 by ELISA Western blotting analysis	Suppressed IL-1β-induced production of NO and PGE_2 Reduced iNOS and COX-2 protein production Decreased the levels of NO and PGE_2 Inhibited IL-1β-induced expressions of matrix metalloproteinase (MMP)-1, MMP-3, MMP-13, and ADAMTS5 in rat chondrocytes Suppressed the IL-1β-induced MAPK pathway activation	[140]
Sinapic acid	Gentamicin-induced nephrotoxicity 10 and 20 mg/kg Inflammation markers: NF-κB (p65), TNF-α, IL-6, and MPO, apoptotic markers (caspase 3, Bax, and Bcl-2) were measured by ELISA, Western blot analysis and histopathological examination	Decreased TNF-α levels by 0.8- and 0.36-fold and IL-6 levels by 0.61- and 0.49-fold compared to gentamicin-induced nephrotoxic rats Significantly decreased NO content in a dose-dependent manner Significantly reduced the expression of the nuclear protein NF-κB (p65) and DNA-binding activity with elevated IκBα Prevented the elevation in MPO activity	[141]
Ferulic acid	Mice exposed to chronic unpredictable mild stress Measurement of proinflammatory cytokines, NF-κB Nucleotide binding and NLRP3 inflammasome ELISA Western blotting PCR Tail suspension test	Significantly increased sucrose preference Decreased immobility time in tail suspension test Significantly decreased IL-1β and TNF-α mRNA expression in the prefrontal cortex Inhibited microglia activation in the prefrontal cortex Significantly decreased phosphorylated and total NF-κB levels Significantly decreased IL-1β expression in the serum and prefrontal cortex	[142]
Ferulic acid	Monosodium urate crystal-induced inflammation in rats 30 mg/kg Assay of articular elastase and lysosomal enzyme Assessment of proinflammatory cytokines qRT-PCR analysis Immunohistochemical detection of NF-κB (p65) and TNF-α Histopathological assessment of ankle joints	Decreased paw edema Significantly reduced the levels of articular elastase and lysosomal enzymes Suppressed serum TNF-α and IL-1β levels in rats Decreased transcriptional level of inflammatory cytokines (TNF-α and IL-1β), NLRP3 inflammasomes, caspase-1, and NF-κB (p65) Decreased expression of NF-κB (p65), and TNF-α in the ankle joint sections	[143]
Ferulic acid	Formaldehyde-induced hepatotoxicity Measurement of TNF-α, IL-6, IL-1β, IL-8 and YKL-40 by ELISA Histopathological evaluation	Significantly decreased IL-6, TNF-α, IL-1β, IL-8, and YKL-40	[144]
Ferulic acid	Cell culture rat vascular smooth muscle cells (VSMCs) Measurement of IL-6, IL-1β, and TNF-α levels by ELISA Analyzed the iNOS mRNA expression levels in VSMCs by RT-PCR Western blot analysis Evaluated the ERK1/2, p38MAPK, JNK, AKT, and NF-κB activation	Significantly decreased the IL-6, IL-1β, and TNF-α levels Inhibited iNOS gene expression in H_2O_2-induced VSMCs Reduced H_2O_2-induced iNOS mRNA expression Significantly decreased p22phox, p47phox, and gp91phox mRNA expression Significantly reduced gp91phox, p47phox, and NOX4 protein levels in H_2O_2-induced VSMCs	[145]
Caffeic acid	Cardiac tissue of diabetic mice Measurement of the levels of IL-1β, IL-6, TNF-α, IL-4, IL-10, and MCP-1 by ELISA Evaluated the cardiac mRNA expression of catalase, GPX1, SOD, IL-1β, IL-6, TNF-α, and MCP-1 by RT-PCR	Significantly lowered cardiac levels of malondialdehyde, reactive oxygen species, interleukin IL-β, IL-6, TNF-α, and MCP-1 Retained cardiac activity of glutathione peroxidase (GPX), superoxide dismutase (SOD), and catalase Significantly upregulated cardiac mRNA expression of GPX1, SOD, and catalase Significantly down-regulated IL-1β, IL-6, TNF-α, and MCP-1 mRNA expression in diabetic mice	[146]

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Table 4 (*continued*)

Molecules	Experimental approach	Key results	Refs.
Caffeic acid	Apolipoprotein E deficient mice (ApoE KO mice)	Significantly reduced the presence of atherosclerotic plaque Reduced expression of markers for macrophages, lymphocytes (both Th1 and Th2), MCP-1, MIP-1, CCR1, CCR2, and ET1 in the vascular wall	[147]
Caffeic acid	Carrageenan-induced edema model Cell culture: RAW 264.7 cells MTT assay Western blot analysis Measurement of PGE_2 and TNF-α using ELISA	Inhibited NO and PGE_2 production Significantly decreased TNF-α Inhibited the protein and mRNA expression levels of iNOS and COX-2 Inhibited NF-κB activation induced by LPS Inhibited iNOS, COX-2, and TNF-α expression by downregulating NF-κB binding activity	[148]
Caffeic acid	LPS-induced NO production in RAW 264.7 macrophages Cell culture: Cell line RAW 264.7 Nitrite assay SNAP-derived NO assay Western blot analysis NOS activity Mouse paw edema Measurement of paw IL-1β levels and myeloperoxidase activity	Inhibited nitrite accumulation on the supernatant of stimulated cells with IC_{50} values of 21.0, 12.0, 8.4, 2.4, 10.7, and 4.80 mM for methyl, ethyl, butyl, octyl, benzyl, and CAPE, respectively Significantly inhibited LPS-induced iNOS expression in RAW 264.7 macrophages Inhibited carrageenan-induced paw edema Prevented the increase of IL-1β levels in the mouse paw Prevented carrageenan-induced neutrophil influx in the mouse paw	[149]
Caffeic acid	LPS-challenged macrophages (RAW 264.7) Cell culture: Cell line RAW 264.7 Measurement of TNF-α and IL-6 protein concentration by ELISA PCR analysis	Significantly reduced mRNA and protein levels of iNOS, TNF-α, and IL-6 Decreased the translocation of the NF-κB/Rel-like containing protein 65 into the nucleus	[150]
Caffeic acid	Streptozotocin-induced diabetic mice Determination of renal cytokines	Suppressed the renal aldose reductase mRNA expression Lowered renal levels of IL-6, IL-1β, TNF-α, and MCP-1 Downregulated the TNF-α and MCP-1 mRNA expression in kidney	[151]
Caffeic acid	Imidacloprid (IMI)-induced hepatotoxicity Western blot analysis Measurement of oxidative stress biomarkers Terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling (TUNEL) assay	Downregulated the liver NO generation and lipid peroxidation Upregulated the glutathione, CAT, SOD, and GPx in a dose-dependent manner in the liver of IMI-induced mice Downregulated the upregulation of TNF-α and IFN-γ induced by IMI in mice liver Significantly decreased positive apoptotic hepatocytes	[152]

6.3.2. Epicatechin

Epicatechin is another flavonoid compound that shows an anti-inflammatory effect both in vitro and in vivo. Several studies revealed that epicatechin regulated the inflammatory process in the LPS-induced production of proinflammatory mediators in RAW 264.7 cells [159–161]. In a study reported by Wang and Cao [159], epicatechin inhibits the production of proinflammatory mediators, such as NO, PGE_2, TNF-α, and IL-6, in LPS-induced RAW 264.7 macrophages. This compound reduces nitrite, PGE_2, and other proinflammatory cytokines (IL-1β, IL-6, and TNF-α) in RAW 264.7 cells [160]. This inhibition is associated with several molecular mechanisms, especially the downregulation of translocated levels of p50 and p65 and IKK α/β phosphorylation levels in RAW 264.7 cells, resulting in NF-κB activation [160]. Using the same approach, Chiou et al. [161] showed that epicatechin attenuated ROS levels and suppressed LPS-induced iNOS and COX-2 expression. This flavonoid interferes with the cross-talk between NF-κB and nuclear factor erythroid-derived factor 2-related factor 2-antioxidant response element (Nrf2-ARE) signaling, therefore activating Nrf2 and suppressing NF-κB, which represses proinflammatory mediators [161]. In the carrageenan-induced paw edema model, epicatechin suppresses induced inflammation and exhibits an anti-inflammatory effect at 100 mg/kg (59%) [162]. Furthermore, quercetin suppresses the writhing response in mice and reduces the expression levels of PGE_2, TNF-α, IL-1β, and IL-6 [163]. In another investigation employing diet-induced human-CRP and NF-κB in vivo, epicatechin quenches the formation of the liver-derived pro-atherogenic factors, serum amyloid A and human-CRP, and inhibits diet-inducs NF-κB activity [164]. In obese mice (after HFD consumption-induced inflammation in C57BL/6J mice), epicatechin prevents HFD-induced increases in TNF-α and MCP-1 in the visceral adipose tissue. Quercetin inhibits palmitate-induced increase in IL-6 and TNF-α secretion and decreases adiponectin secretion [165]. Epicatechin alleviates HFD-induced oxidative and endoplasmic reticulum stress by inhibiting NADPH oxidases (NOX-4 and NOX-2) in the visceral fat of HFD-fed mice [165].

6.4. Alkaloids

Alkaloids have been detected in some Moroccan medicinal plants that possess anti-inflammatory and analgesic activities. One example is *D. staphysagria* containing diterpenoid alkaloids as the main active compounds [27]. Alkaloids have shown an anti-inflammatory effect involving several mechanisms of action [42,166], including the inhibition of inflammatory mediators such as interferon-γ, TNF-α, IL-12, and also via a specific inhibitory effect on certain enzymes involved in the inflammatory process such as LOX and COX [166].

7. Insights into the analgesic mechanism of bioactive compounds isolated from Moroccan medicinal plants

7.1. Volatile compounds

Various terpenoids have been identified in analgesic Moroccan medicinal plants, including α-pinene, thymol, limonene, linalool, isopulegol, carvacrol, camphor, phenol-camphor, and bornyl acetate (Table 5) [88,167–180]. Bornyl acetate was assessed for its analgesic effect using in vivo models [171,172]. Using hot plate and writhing reaction assays, Wu et al. [171] reported that bornyl acetate reduced the writhing reaction induced by glacial acetic acid and reduces the pain caused by the hot plate.

Bornyl acetate was also evaluated using the tail clip and formalin models of pain, inhibiting phases I and II pain in formalin-induced pain model [171]. In another study using the same experimental methods, bornyl acetate exhibits a marked inhibitory effect on phases I and II pain in the formalin-induced pain model, with a pronounced analgesic effect afforded against pain induced by the tail clipping model [171]. Conversely, carvacrol shows an analgesic effect against formalin-, capsaicin-, and glutamate-induced orofacial nociception in mice administered at 25, 50, and 100 mg/kg i.p. Carvacrol reduces the nociceptive face-rubbing behavior and produces a pronounced antinociceptive effect at all investigated doses

[170]. The analgesic effect of isopulegol was evaluated using acetic acid-induced writhing and hot plate tests [169]. The administration of isopulegol at 0.5, 1, 5, 10 mg/kg exhibits significant analgesic activity as demonstrated by the percentage of pain inhibition (7.4% ± 1.3%) at 0.5 mg/kg and the percentage of pain protection (20.3% ± 2.2%) (Table 5). Linalool is another monoterpene detected in some Moroccan medicinal plants, which was evaluated for its anti-inflammatory effects using the formalin-inflamed mouse hind paw model, thermal nociceptive threshold, and plantar analgesia measured at different time points [167]. The results showed that this volatile compound exhibited superior and faster lowering of swelling and pain. In contrast, the anti-inflammatory effect of limonene was evaluated using the pain-related behavior model by administering intraplantar H_2O_2 [168]. Limonene reduces the total number of nociceptive behaviors when compared with mice treated with the vehicle and suppresses TRPA1-mediated oxidative stress-induced nociception [168].

7.2. Flavonoids

Some flavonoids identified in Moroccan medicinal plants, such as quercetin, quercetin-3-methoxy-40-glucosyl-7-glucoside, and epicatechin gallate, have shown potent analgesic activities in vivo [175–179]. Quercetin was tested against potassium antimony tartrate and electrically stimulated vocalization in mice (50–200 mg/kg) (Table 5). It reduces the writhing numbers and raises the vocalization threshold peak at 200 mg/kg [175]. In another study, quercetin inhibits foot pain and increases the pain threshold, demonstrating analgesic effects [176]. Quercetin improves the pain threshold and reduces the stretching time in mice assessed using acetic acid and the hot plate tests [177]. Quercetin-3-methoxy-40-glucosyl-7-glucoside was evaluated for its analgesic effect by employing acetic acid-induced writhing, hot plate, and tail-flick models [178]. At doses of 5, 10, or 15 mg/kg, quercetin inhibits the pain threshold (73.1%) in the acetic acid-induced

Table 5
Analgesic mechanism insights of bioactive compounds isolated from Moroccan medicinal plants with analgesic effects.

Chemical families	Molecules	Experimental approach	Key results	Refs.
Volatile compounds	Thymol	Eddy's hot plate method	Significant analgesic effect at 240 min	[88]
	Camphor	Eddy's hot plate method	Significant analgesic effect at 240 min	[88]
	α-Pinene	Formalin-inflamed mouse hind paw model Thermal nociceptive threshold Plantar analgesia measured at different time points	Exhibited greater and faster lessening of swelling and pain	[167]
	Limonene	Pain-related behaviours caused by intraplanar injection of H_2O_2	Significantly reduced the total number of nociceptive behaviors compared to mice treated with the vehicle Suppressed TRPA1-mediating oxidative stress-induced nociception in vivo	[168]
	Linalool	Formalin-inflamed mouse hind paw model Thermal nociceptive threshold Plantar analgesia measured at different time points	Exhibited greater and faster lessening of swelling and pain	[167]
	Isopulegol	Acetic acid-induced writhing test Hot plate test 0.5, 1.5, and 10 mg/kg	Exhibited analgesic activity in both tests Optimal dose=1 mg/kg Percentage of pain inhibition=7.4 ± 1.3 at a dose of 0.5 mg/kg Percentage of protection=20.3 ± 2.2	[169]
	Carvacrol	Formalin-, capsaicin-, and glutamate-induced orofacial nociception in mice 25, 50, and 100 mg/kg i.p.	Reduced the nociceptive face-rubbing behavior Produced a significant antinociceptive effect at all doses	[170]
	Bornyl acetate	Pain models induced by tail clipping method Pain model caused by formalin test	Induced analgesic effects on pain models induced by tail clipping method Inhibited phases I and II of pain in formalin-induced pain model animals	[171]
	Bornyl acetate	Pain models induced by tail clipping method Pain model caused by formalin test	Inhibited phases I and II of pain in formalin-induced pain model animals Produced obvious analgesic effects in pain models induced by pressing tail	[171]
	Bornyl acetate	Hot-plate and writhing reaction method	Restrain writhing reaction caused by acetic acid glacial Reduced pain caused by hot plate	[172]
		Acetic acid writhing test in mice	Antinociceptive action of camphor oxime derivatives	[173]
	Phenol-camphor	In 82 patients with alveolitis and loosely filled alveoli, gauze impregnated with the phenol-camphor solution was applied	Pain was moderated by phenol-camphor The effect of the phenol-camphor solution lasted 6–8 h	[174]
Flavonoids	Quercetin	Potassium antimony tartrate and the vocalization stimulated by electricity in mice at 50–200 mg/kg	Reduced the writhing numbers and increased the vocalization threshold peak at 200 mg/kg	[175]
		Hot plate test	Inhibited the foot pain Increased pain threshold and analgesic pain killer	[176]
		Acetic acid and the hot plate tests	Improved pain threshold and reduced the stretching time in mice	[177]
	Quercetin-3-methoxy-40-glucosyl-7-glucoside	Acetic acid-induced writhing method Hot plate method Tail-flick test 5, 10 or 15 mg/kg	73.1% inhibition of the pain threshold in acetic acid-induced writhing model Prolonged the reaction time of the animals undergoing the hot plate and Tail-flick tests	[178]
	Epicatechin gallate	Hot plate method The responses at 0, 60, 120, 180, 240, and 300 min with 100, 200, and 400 mg/kg body weight	Increased the reaction time Maximum analgesic effect after 120 min treatment The 400 mg/kg dose was insignificant to the diclofenac sodium-treated group	[179]
Phenolic acids	Ferulic acid	Thermal hyperalgesia and mechanical allodynia tests CCL mice Behavior and neurobiological analysis 10, 20, 40 and 80 mg/kg p.o.	Increased heat sensation and nociceptive threshold Increased 5-HT and norepinephrine levels in hippocampus, frontal cortex and amygdale and could inhibit monoamine oxidase-A activity in mouse brains	[180]

writhing model. Furthermore, it prolongs the reaction time of the animals during the hot plate and tail-flick tests [178]. Epicatechin gallate suppresses inflammation induced by the hot plate method. The administration of epicatechin gallate at 100, 200, and 400 mg/kg body weight increases reaction time, showing a maximum analgesic effect after 120 min of treatment [179].

7.3. Phenolic acids

Only one molecule belonging to phenolic acids was isolated from Moroccan plants and investigated for potential analgesic effects (Table 5) [180]. Using thermal hyperalgesia and mechanical allodynia tests, as well as behavioral and neurobiological analysis in mice, ferulic acid, at 10, 20, 40, and 80 mg/kg p.o., increases the mechanical allodynia and nociceptive threshold. Ferulic acid increases 5-HT and norepinephrine levels in the hippocampus, frontal cortex, and amygdala and decreases monoamine oxidase (MAO)-A activity in mouse brains [180].

8. Clinical evidence

The clinical evaluation of natural antidiabetic substances is a necessary step to discover novel antidiabetic drug leads. The bioactive molecules identified in Moroccan plants with inflammatory properties have been evaluated in humans. Researchers assessed these substances in patients or healthy individuals, with some compounds currently under investigation in different clinical trials at different phases. The results reported in previous studies are presented in Table 6 [72,181–193], which summarizes the name of the molecule, the experimental approach, the clinical phase, and major results. Several molecules, especially those belonging to the flavonoid class of compounds, have been evaluated.

In clinical investigations, quercetin is the most frequently investigated molecule for its anti-inflammatory properties. This molecule has been assessed in several clinical trials and is undergoing phase III trials. McAnulty et al. [183] showed that quercetin ingestion does not exert protection from exercise-induced oxidative stress and inflammation. However, increasing the quercetin plasma concentration inhibited the generation of inflammatory mediators such as cytokines and chemokines. Moreover, in the field of athletics, Konrad et al. [186] revealed that this molecule significantly decreased the expression of numerous inflammatory factors and mediators. Indeed, quercetin decreases CRP levels, GM-CSF, and interleukins (IL-10, IL-1b, IL-2, IL-6, and IL-8). However, acute ingestion of quercetin did not exhibited inflammatory or immune changes relative to placebo. In another report [188], quercetin significantly increases the level of IL-8 and CRP following exercise. In another work, results showed that physical activity resulted in significant increases in CRP, GM-CSF, IL-10, IL-1β, IL-2, IL-6, IL-8, and TNF-α. However, acute ingestion of quercetin 15 min before strenuous exercise caused a sharp increase in plasma quercetin levels, but did not counteract either the immune response or post-exercise inflammation compared to the placebo effect [186]. Dower et al. [181] investigated the effect of quercetin supplementation on biomarkers of inflammation in (pre) hypertensive adults. Accordingly, quercetin significantly reduces the expression of IL-1β (by 0.23 mg/mL), in a placebo-controlled trial. These results corroborate those reported by Javadi et al. [190], who revealed a significant decrease in the level of highly sensitive TNF-α in women with rheumatoid arthritis. Furthermore, Sajadi Hezaveh et al. [191] recently demonstrated that quercetin affords a protective effect against inflammation in patients with thalassemia. However, additional studies failed to detect any impact on inflammatory markers [184,187] in healthy subjects. In another study performed in 2013 on healthy subjects with the apolipoprotein E genotype, quercetin shows a moderately increased level of TNF-α [189]. Regarding epicatechin, a study by Dower et al. [181] clinically evaluated the anti-inflammatory potential of epicatechin supplementation in healthy women and men with hypertension. The results showed no significant effect on inflammatory markers or the z-score of inflammation. Ferk et al. [182] evaluated the anti-inflammatory action of gallic acid in patients with diabetes. The

Table 6
Clinical evidence of anti-inflammatory activity of bioactive compounds in Moroccan medicinal plants with anti-inflammatory effects.

Molecules	Human subjects	Study type	Effects	Refs.
D-Limonene	Healthy elderly subjects	Phase III	Decreased IL-6 levels	[72]
Epicatechin	Healthy (pre) hypertensive men and women	Phase III	No significant effect on markers of inflammation or z-score for inflammation	[181]
Gallic acid	Patients with diabetes	Phase III	No impact on IL-6 and adiponectin (proinflammatory and anti-inflammatory cytokines)	[182]
Quercetin	Athletes	Phase III	Chronic quercetin ingestion does not exert protection from exercise-induced oxidative stress and inflammation	[183]
	Subjects performing repeated sprint tests	Phase III	No attenuation of xanthine oxidase activity or IL-6	[184]
	Sarcoidosis patients	Phase III	Reduced markers of inflammation (TNF-α/IL-10 and IL-8/IL-10)	[185]
	Athletes	Phase III	Acute ingestion did not counter postexercise inflammation or immune changes relative to placebo	[186]
	Healthy subjects	Phase III	No effect on inflammatory markers after unusual exercise activity (IL-6 and CRP)	[187]
	Athletes	Phase III	IL-8 and CRP increased significantly immediately after exercise	[188]
	Healthy subjects with apolipoprotein E (APOE) genotype	Phase III	Slightly proinflammatory effect (moderately increased levels of TNF-α)	[189]
	Healthy (Pre) hypertensive adults	Phase III	Significantly decreased $\Delta_{quercetin}-\Delta_{placebo}$ for IL-1β by 0.23 pg/mL	[181]
	Women with rheumatoid arthritis (RA)	Phase III	Significantly reduced high sensitivity TNF-α level	[190]
	Patients with thalassemia	Phase III	Effect on inflammation was indistinctive Reduced high sensitivity (hs)-CRP and ferritin No significant effect on TNF-α	[191]
Ferulic acid	Hyperlipidemic subjects	Phase III	Significantly reduced the inflammatory markers hs-CRP (32.66%) and TNF-α (13.06%)	[192]
	Normal subjects			[193]
Sinapic acid	Normal subjects	Phase II	Important immunomodulatory effect with systemic bioavailability	[193]
Vanillic acid	Normal subjects	Phase II	Important immunomodulatory effect with systemic bioavailability	[193]
Caffeic acid	Normal subjects	Phase II	Important immunomodulatory effect with systemic bioavailability	[193]
p-Hydroxy benzoic acid	Normal subjects	Phase II	Important immunomodulatory effect with systemic bioavailability	[193]

results revealed that gallic acid consumption (15 mg/day) for seven days significantly reduced CRP (by 39%) but had no effect on IL-6 and adiponectin. In a clinical study by Bumrungpert et al. [192], patients with hyperlipidemia received ferulic acid supplementation and showed an attenuation of the inflammatory marker TNF-α (13.06%) and hs-CRP (32.66%).

9. Conclusions and perspectives

In the present review, we revealed that Moroccan medicinal plants possess anti-inflammatory and analgesic effects, with significant heterogeneity depending on the medicinal species, the type of extracts and/or essential oils, and assay methods employed. The anti-inflammatory and analgesic effects appear to be associated with the medicinal plant's secondary metabolites, such as flavonoids, alkaloids, and terpenes. These bioactive compounds have presented an anti-inflammatory effect through numerous targeted pathways, particularly by inhibiting mediators involved in inflammatory processes. Other mechanisms of action were discussed, including the deregulation of gene expression of some transcriptional factors promoting inflammation-related signaling pathways. These data suggest that Moroccan medicinal plants are rich in bioactive molecules, which could be a promising resource for identifying new anti-inflammatory and analgesic drugs. However, further investigations exploring additional Moroccan medicinal plants for their anti-inflammatory and analgesic effects are warranted. Furthermore, the identification and isolation of different bioactive compounds from these medicinal species should be undertaken. Finally, in vitro and in vivo molecular investigations of these substances, as well as their clinical validation, will undoubtedly contribute to uncovering novel drugs from Moroccan medicinal plants possessing anti-inflammatory and analgesic properties.

CRediT author statement

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

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