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# Natural Products as a Source for Novel Analgesic Compounds

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Rehab Fawzy Abdel-Rahman

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## Abstract

Natural products have an important role in the discovery of analgesic drugs along with the determining of the complex mechanisms involved in pain transmission and pain relief. Lately, several substances with antinociceptive actions have been purified from natural sources and further identified, resulting in novel structural classes and more understanding of the underlying pharmacological mechanisms of actions. Yet, natural products still hold great potential for the discovery of novel agents for treatment of pain disorders and potentially drug addictions with exciting pharmacological profiles (i.e. no side effects, no addictive potential). The aim of this chapter is to highlight some active compounds derived from natural sources that possess analgesic properties. Additionally, the identification of new compounds derived from natural sources could lead to great understanding of the underlying pharmacological mechanisms of action, which will be addressed in this chapter as well.

**Keywords:** plant-derived compounds, analgesic properties, pharmacological mechanisms of action

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## 1. Introduction

At the present time, many formulas for the relief of pain are present; among them, medicinal herbs are highlighted because of their wide popular use and availability. Many plant-derived compounds could offer valuable therapeutic effects for the treatment of chronic inflammatory conditions, which are likely associated with pain.

In the drug market today, about 40% of all medicines have been originated directly or indirectly from natural sources. It is estimated that about 25% being derived from plants, 13% from microorganisms and 3% from animals. For instance, morphine, salicin, artemisinin,

capsaicin, atropine, pilocarpine, digitalis, quinine, scopolamine and captopril are examples of drugs derived from natural sources [1, 2].

## 2. Active compounds derived from natural sources possessing analgesic properties

Since ancient times, many active compounds originated from natural sources have been consumed for various medical purposes including the management of pain. Opium, for example, has been used since 7000 years ago. Up to the nineteenth century, other active components derived from different natural remedies were identified, purified and utilized. Since then, analogues have been made from natural sources, and completely synthetic compounds based on natural pharmacophores have been introduced into the market [3].

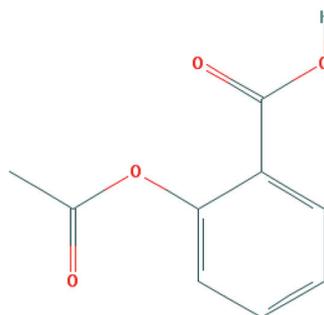
### 2.1. Aspirin

Aspirin or acetylsalicylic acid (**Figure 1**) is extracted from the bark of the Willow tree *Salix alba*, family *Salicaceae*. It is one of the most extensively used analgesic agents for the management of mild pain. Aspirin is considered the first nonsteroidal anti-inflammatory drug (NSAID) that inhibits the arachidonic acid pathway resulting in the synthesis of eicosanoids, which is a potent pain mediator [4]. Moreover, the inhibition of the cyclooxygenase (COX) enzymes by aspirin led to the discovery of other synthetic NSAIDs.

For instance, the study of the biochemical cascade of COX system led to the discovery of the COX-2 enzyme inhibitors. COX-2 inhibitors are believed to be safer than other NSAIDs that inhibit the COX-1 enzyme. Rofecoxib (Vioxx)<sup>®</sup> is an example of a compound that selectively targets the COX-2 enzyme, and it was voluntarily withdrawn by Merck and Co., Inc. on September 30, 2004, from the US drug market due to an increased risk of cardiovascular effects [5].

### 2.2. Opioids

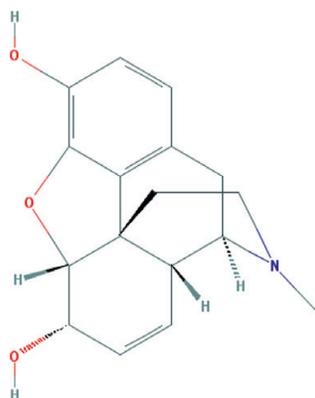
Natural opiates and synthetic opioids are potent analgesics that bind to receptors for endogenous opiates in the central nervous system (CNS). Opioid is the common name for all com-



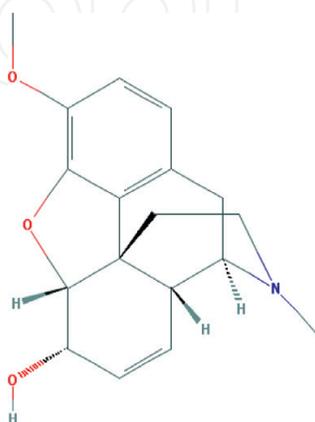
**Figure 1.** Aspirin.

pounds acting on opioid receptor as the constituents of opium, to produce morphine-like effects. *Papaver somniferum* (family: *Papaveraceae*) is one of the oldest medicinal plants known by mankind, and abuse of its opium juice has been known before history was recorded. Opium contains about 25 alkaloids, including morphine (**Figure 2**), codeine (**Figure 3**) and thebaine (**Figure 4**) [6]. Tramadol is a synthetic analogue of codeine that acts by binding to  $\mu$  (mu) opiate receptors, added to that it inhibits norepinephrine and serotonin reuptake [7]. Whereas, by modifying the chemical structure of thebaine, a semisynthetic derivative is obtained, termed oxycodone [8]. The endogenous opioid receptor system includes four receptor subtypes designated as mu ( $\mu$ ), delta ( $\delta$ ), kappa ( $\kappa$ ) and opioid receptor like (ORL-1) receptors. These receptors are widely disseminated in the mammalian system and have been found in all vertebrates. Opioid receptors are highly distributed in the CNS, including the brain and spinal cord, but they are also found in the gastrointestinal system and in the cells of immune system [9].

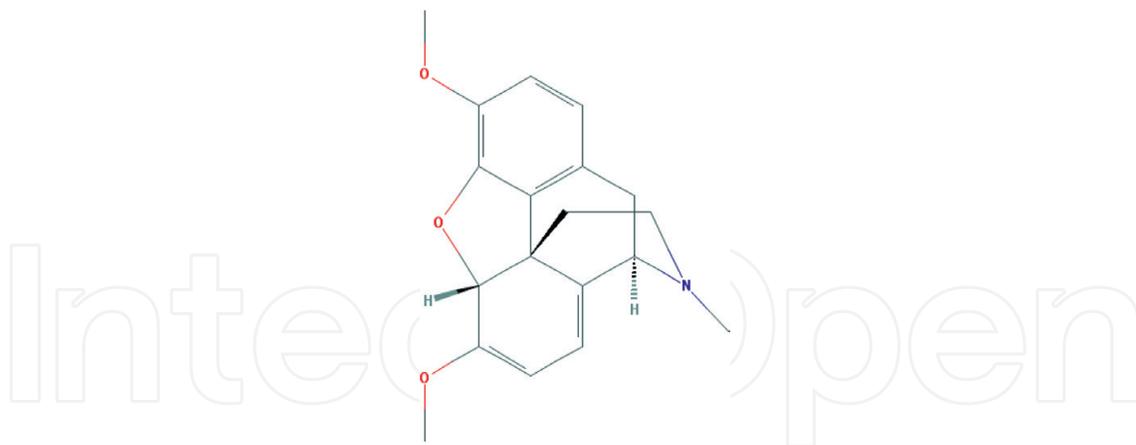
Lately, newly discovered chemical structures have appeared in the literatures that interact either with opioid receptors directly or through some other mechanism of controlling opioid receptor signalling. These compounds are interesting from a drug design perspective as most of them do not contain nitrogen.



**Figure 2.** Morphine.



**Figure 3.** Codeine.



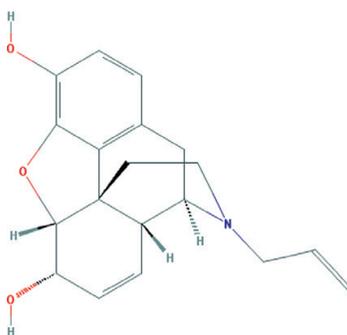
**Figure 4.** Thebaine.

### 2.2.1. Morphine

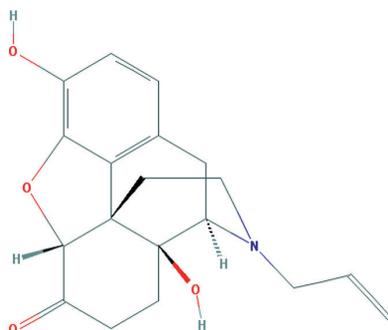
In the 1850s, morphine began to be used for chronic pain, in minor surgical operations and after surgery. Morphine is the most abundant opiate obtained from opium. It is the dried latex obtained by shallow slicing of the unripe seedpods of *Papaver somniferum*. Meperidine was the first synthetic opioid analgesic, with a completely different structure from that of morphine, and its analgesic properties were identified in 1939. Far ahead in 1942, nalorphine was obtained, as the first opioid receptor antagonist, by replacing the substituent group on the nitrogen atom. By replacing the allyl group with the methyl group, nalorphine (**Figure 5**) is obtained from morphine, and naloxone is obtained from oxymorphone (**Figure 6**) [10, 11].

Nalorphine acts as an antagonist at the  $\mu$  and  $\delta$  receptors, but it acts as a weak agonist at the  $\kappa$  receptor, and thus gives slight analgesia. However, nalorphine has hallucinogenic side effects. Whereas, naloxone is an antagonist at the three opioid receptors ( $\mu$ ,  $\delta$  and  $\kappa$  receptors). This compound is used to elucidate the possible roles of opioids in response to stress [11, 12].

In spite of the remarkable efforts by researchers to discover safe, effective and nonaddictive opioids for pain treatment, morphine remains the most valuable painkiller in contemporary medicine [13].



**Figure 5.** Nalorphine.



**Figure 6.** Naloxone.

The pharmacological properties of morphine are somewhat complex and varying according to the dose, site of action, route of administration and animal species. Morphine is mostly considered as pain perception modifier, resulting in an increase in the threshold of painful stimuli. Nowadays, analgesia induced by morphine is known to be mediated via activation of membrane opioid receptors, and consequently, it can be inhibited by opioid receptor antagonists, as naloxone. Furthermore, certain undesirable side effects of morphine as euphorogenic effect, inhibition of gastrointestinal transit time, constipation, loss of appetite, hypothermia, bradycardia and retention of urine seem to involve receptor-mediated actions [14].

As more chemical components of traditionally used plants for the treatment of pain are elucidated, there is a great potential for the development of novel drug treatments acting through opioid receptors. Indeed, some newly discovered chemical structures have been published in the literatures that interact either directly with opioid receptors or through some other mechanisms of controlling opioid receptor signalling. In the next section, examples of some of those chemical structures will be reviewed.

### 2.2.2. Menthol

Menthol (**Figure 7**) is isolated from peppermint (*Menthapiperita*, family: *Lamiaceae*). For many centuries, menthol was utilized as an antipruritic, antiseptic and a coolant in topical preparations as it causes a feeling of coolness due to stimulation of 'cold' receptors by inhibiting  $\text{Ca}^{2+}$  currents of neuronal membranes. It has also been reported that modulation of  $\text{Ca}^{2+}$  currents is involved in the regulation of pain threshold. Indeed, the inhibition of  $\text{Ca}^{2+}$  currents by administration of voltage-sensitive  $\text{Ca}^{2+}$  channel blockers can produce antinociception in laboratory animals. Lately, it was evaluated in the hot plate and acetic acid writhing tests where it revealed potent activity through interaction with opioid receptors, and more selectively, kappa opioid receptors activation [15].

### 2.2.3. Salvinorin A

Salvinorin A (**Figure 8**), isolated from *Salvia divinorium* (*Lamiaceae*, formerly *Labiatae*), was first described in nonnitrogenous selective kappa opioid receptor ligand. Salvinorin A acts as kappa opioid receptors agonist in spinally mediated pain. There is a great attention for kappa opioid

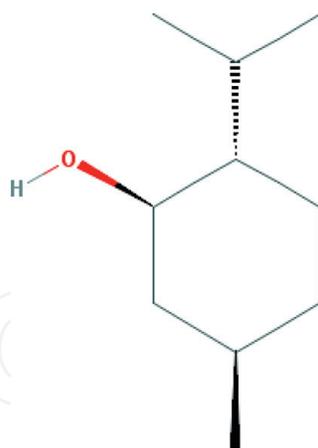


Figure 7. Menthol.

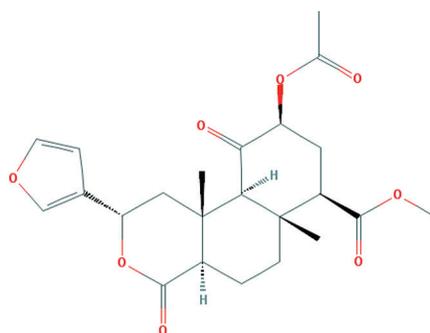


Figure 8. Salvinorin A.

receptor agonists among the pharmaceutical industry field [3, 16]. The ethnopharmacological uses of *Salvia divinorum* extract leaves being used to relieve headaches, as a sedative, and for the treatment of some gastrointestinal disorders since the anatomical location of  $\kappa$  opioid receptors in brain, spinal cord, GI tract, etc [17].

Unfortunately,  $\kappa$  opioid receptor agonists produce unwanted side effects; thus, they are not commonly prescribed as analgesics. In this consent, salvinorin A has been reported to cause dysphoric hallucination when administered in human [18, 19]. Nonetheless, it is still listed as a chemical of concern by the United States Drug Enforcement Agency and is currently allowed to be marketed as alternative to other illegal hallucinogens.

#### 2.2.4. Mitragynine

Mitragynine is a nitrogen-containing compound with a unique structure. It is derived from the traditional Thai herb *Mitragyna speciosa* (*Rubiaceae*). The herb has been used for many years in Thailand as a replacement for opium and used by drug addicts seeking for relief during opioid withdrawal stage. However, the use of *M. speciosa* is currently illegal in Thailand, Malaysia, South Korea and Australia, but widely available in the United States and UK [20–22].

At least two compounds have been identified in *M. speciosa* by Takayama “in Ref. [23]”, both having opioid receptor activity. The first compound termed mitragynine (**Figure 9**) is one of the

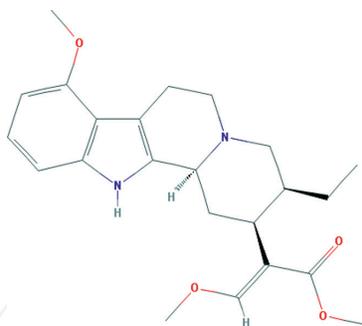


Figure 9. Mitragynine.

major alkaloidal components. It is a corynanthe based acting as a partial opioid receptor agonist, with about 26% the activity of morphine. The other and the more interesting compound is 7-hydroxymitragynine (mitragynine hydroxyindolenine) (Figure 10), with activity of 1000 times or more than that of morphine.

Mitragynine is ingested orally by chewing fresh leaves or by drinking a tea brewed with the substance. The medicinal properties of this plant had been previously described in combating fatigue and to tolerate hard work, due to its opium-like effect at high doses and cocaine-like stimulant effect at low doses. However, death was reported as a result of mitragynine abuse [24, 25].

### 2.3. Capsaicin

Capsicum genus, which produces both chilli peppers and bell peppers, belong to the family of *Solanaceae*. Capsicum is originated in Central and South America and has more than 20 species that are widely spread around the world. Indeed, only five species are widely cultivated including: *C. annuum*, *C. chinense*, *C. frutescens*, *C. pendulum* and *C. pubescens* [26].

It seems that capsicum species are among the oldest cultivated plants in the world (5200–3400 BC). Scientists have found an evidence of people who consumed peppers in Mexico as early as 7000 BC; this was the oldest document of capsicum use [27]. Högyes (1878) was the first to make evident that the alcoholic extract of paprika (*Capsicum annuum*) resulted in hypothermia when administered systemically [28].

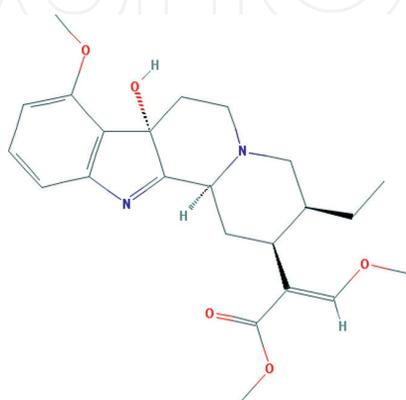


Figure 10. Mitragynine hydroxyindolenine.

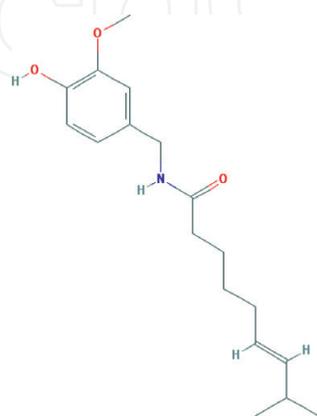
Interestingly, the study of pungent principles began in the 1810s using the names “capsicol”, “capsicin”, “capsacutin”, etc. Later, capsaicin is the active principle isolated from *Capsicum* species by Thresh in 1846 [29] (**Figure 11**). The exact chemical structure of capsaicin was identified after half a century by Nelson in 1919 [30]. Capsaicin is considered as the most prominent component in plants belonging to *Capsicum* species, with about 70% of the total pungent acid amides and 30% or less constituting dihydrocapsaicin, an analogue of capsaicin (capsaicinoid) [14, 31].

Despite the unwanted primary irritant effect of capsaicin to the mucous membranes and the eyes, it is used clinically for the management of neuropathic pain syndromes and arthritis [1, 3]. The Native Americans used *Capsicum* to treat cramps, diarrhoea and indigestion. Other folk medicinal uses of capsaicin include enhancement of appetite, treatment of gastric ulcers, rheumatism and restoration of hair growth [32].

The biological effects of capsaicin (8-methyl-*N*-vanillyl-6-nonenamide) are biphasic: first by the excitation of the primary afferents and the second phase involves desensitization or inactivation of neurons [33]. Capsaicin stimulates the afferent sensory neurons that conduct the nociceptive information to the central nervous system (CNS), precisely the C and A $\delta$  fibres. The stimulatory effect is mainly through calcium influx, the release of several neuropeptides including tachykinins, calcitonin gene-related peptide (CGRP) and somatostatin. It also blocks the intra-axonal transport of macromolecules, such as the neural growth factor (NGF) [27]. Additionally, capsaicin is a vanilloid receptor -1 (VR1) agonist. It is known to have an inhibitory effect on nitric oxide (NO $x$ ) production in macrophages; this effect clarifies its implications in the pathogenesis of inflammatory diseases [3, 34].

#### 2.4. Aconitum alkaloids

*Aconitum* species, family *Ranunculaceae*, known by different names such as aconite, monkshood, wolf’s bane, women’s bane, Devil’s helmet or blue rocket. *Aconitum* plants (mainly *A. japonicum* Thunberg and *A. carmichaeli* Debeaux) have been used from the time of historic civilizations in Ayurvedic, Chinese, Tibetan and Greco-Roman medicines for their various



**Figure 11.** Capsaicin.

pharmacological effects. Plants of *Aconitum* genus were familiar in the European countries' medicine in the nineteenth century [35].

Leaves and roots of *Aconitum* plant were used to relieve neuralgic pain, particularly in the face to relieve the pain of sciatica. The root is extremely bitter; its paste is applied in acute rheumatism also on cuts and wounds as an anti-inflammatory and antiseptic agent [36].

There are two groups of *Aconitum* alkaloids revealing strong to moderate analgesic properties. The first group includes aconitine-like diester alkaloids with strong analgesic activity: aconitine (**Figure 12**), hypaconitine, mesaconitine, 3-acetylaconitine, bulleyaconitine, and yunaconitine. The second group involves less-toxic alkaloids having moderate analgesic effect. One of them, lappaconitine (**Figure 13**), it is believed that lappaconitine and its deacetylated analogue have lower toxicity than aconitine and, consequently, it is assumed to be safely used as analgesic or anaesthetic agents [35].

Aconitine, 3-acetylaconitine and hypaconitine revealed high affinity  $\text{Na}^+$  channel ligands, thus having antinociceptive, strong arrhythmogenic effects and high acute toxicity, and induce a blockade of neuronal conduction by a permanent cell depolarization. In contrast, lappaconitine has lower affinity for  $\text{Na}^+$  channel and thereafter has lesser antinociceptive and lesser cardiotoxic activity, acting as a local anaesthetic. Other alkaloids with lower  $\text{Na}^+$  channel affinity such as lappaconidine and oxydelcorine have no antinociceptive effect

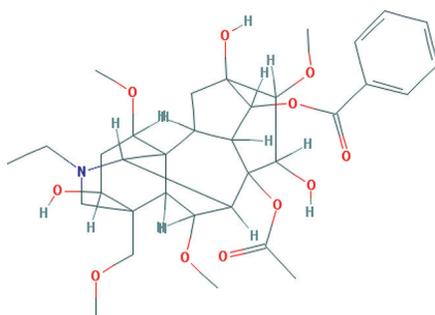


Figure 12. Aconitine.

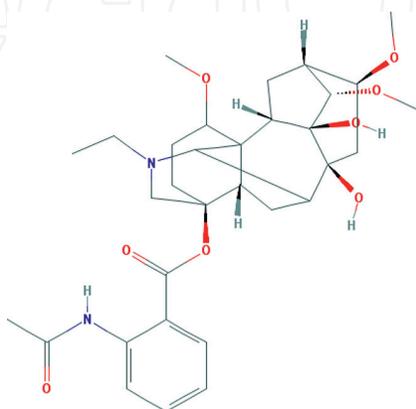


Figure 13. Lappaconitine.

[37]. Despite the large number of alkaloids isolated and identified from *Aconitum* sp. with antinociceptive effect, their cardiotoxic actions hindered their clinical use as analgesics [14].

## 2.5. Polygodial sesquiterpenes

Polygodial sesquiterpene is the major constituent present in the bark of *Drymis winteri* (*Winteraceae*) and related species, a well-known medicinal plant found in some South American countries such as Brazil. *Drymis winteri* is commonly used in folk medicine as an anti-inflammatory and for the treatment of asthma and allergy [38]. Phytochemical investigations of *D. winteri* demonstrated the occurrence of sesquiterpenes, lactones and flavonoids [39, 40].

As well, previous studies [40–42] indicated that a mixture of at least three sesquiterpenes, identified as being polygodial (**Figure 14**), 1- $\beta$ -(*o*-methoxycinnamoyl) polygodial and drimaniol (**Figure 15**), appear to be the main constituents present in the bark of plant *D. winteri* that are accountable for the marked antinociceptive, anti-inflammatory and anti-allergic effects of the crude extract. With regard to the relatively high concentrations of polygodial and to a lesser extent, drimaniol in the bark of *D. winteri*, it can be proposed that the two sesquiterpenes are the most relevant active compounds and are responsible for the major pharmacological activities of the plant.

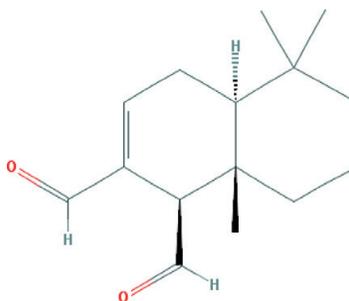


Figure 14. Polygodial.

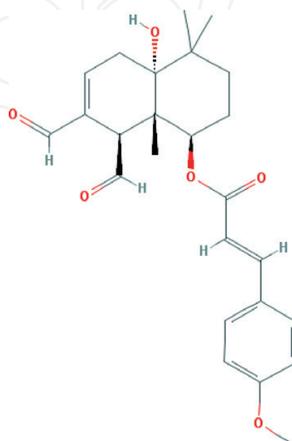


Figure 15. Drimaniol.

The precise site of action by which polygodial induces antinociception is still under investigation. The modulatory role of polygodials as antinociceptives as proposed to be via the interaction with an opiate-like system through  $\kappa$  and  $\delta$  receptors, the  $\alpha_1$ -adrenergic receptor, the serotonergic system, and an interaction with a Gi/o protein pertussis toxin-sensitive mechanism. Thus, polygodial or its derivatives might be concerned in the development of new analgesic drugs for controlling neurogenic pain [40, 43].

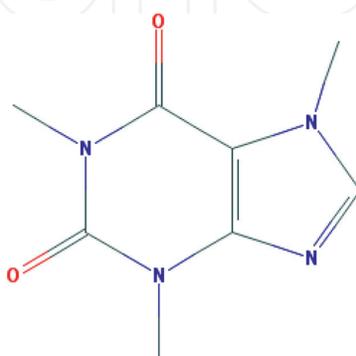
## 2.6. Caffeine

Caffeine is an alkaloid present in over 60 plant species. Caffeine (1,3,7-trimethylxanthine) is mainly in beverages derived from coffee beans, tea leaves and kola nuts (*Cola acuminata*, family: *Sterculiaceae*). Caffeine has been used medicinally together with ergotamine for migraine headaches and in combination with nonsteroidal anti-inflammatory drugs in analgesic preparations [44]. Moreover, caffeine is believed to be potentially effective cancer chemopreventive metabolite in terms of its antioxidant capacity [45].

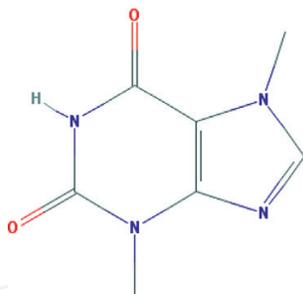
Caffeine was isolated in 1820, but the precise structure of this methylxanthine was established in the last decade of the nineteenth century. Its properties were not fully recognized until 1981, when the stimulating properties of caffeine and its analogues by the blockade of adenosine receptors were allied [46].

Cola nut is native of West Africa, which has been introduced to the West Indies. It is used in large quantities in the soft drink industry. The active principles are caffeine (**Figure 16**) and theobromine (**Figure 17**), which are both stimulants [44].

Caffeine increases alertness, awareness and attention span, has stimulatory effects on mood and sense of wellbeing, and produces an increase in exercise tolerance. Other desirable physiologic effects involve protection of the cerebral vasculature by means of enhancing glucose metabolism. In this concern, it is believed that caffeine consumption has been associated with a reduced risk of Parkinson disease. It also constricts cerebral blood vessels, which is a highly desirable action in patients with migraine [47]. Caffeine is prescribed as a stimulant of the central nervous system and to treat postprandial hypotension and obesity, and also, it is indicated for treatment of apnoea in premature neonates [48].



**Figure 16.** Caffeine.



**Figure 17.** Theobromine.

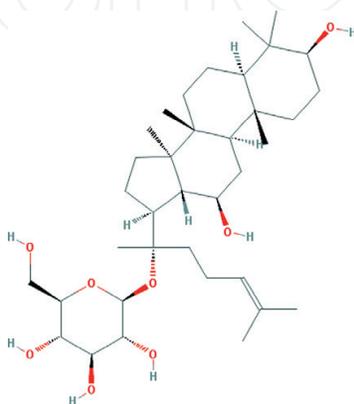
Following oral intake, maximum plasma concentration arises between 30 min and 2 h, which may be prolonged with food ingestion. Caffeine is readily absorbed by the gastrointestinal tract, with 100% bioavailability and high solubility both in aqueous and nonpolar organic solvents. Caffeine is lipophilic with low protein binding. Its plasma protein binding—mainly albumin—is 10–35%. Caffeine rapidly crosses cell membranes, as well as the placental barrier, blood brain, producing drug levels in the brain and cerebrospinal fluid similar to those in plasma [46, 49].

In 1985, Burnstock and Kennedy cited that methylxanthines block purinergic receptors type 1 (P1) and have no effect on P2 receptors [50]. Added to that, the proposed mechanism of action of caffeine seems to be related to the blockade of peripheral and central adenosine receptors involved in the regulation of pain transmission, giving rise to its analgesic properties [14, 51].

## 2.7. Ginsenosides

Ginseng, the root of *Panax ginseng* (*Araliaceae*), has been reported to relieve a variety of ailments. Studies showed that ginseng saponins, which consist of various ginsenosides (**Figure 18**), are the most pharmacologically active constituent of ginseng root. Ginsenosides are believed to be involved in pain modulation as well as in opioid-induced antinociception and tolerance [52, 53].

In traditional folk medicine, ginseng has been used to relieve some types of pain such as toothache, abdominal pain, chest pain and neuralgia. A line of evidence also shows that ginseng



**Figure 18.** Ginsenosides.

saponins are responsible for relieving pain induced by chemicals or noxious heat in experimental animals [54].

Most ginseng species possess active naturally occurring constituents such as the ginsenosides, polysaccharides, peptides, polyacetylenic alcohols and fatty acids. From the ginseng saponin fraction, more than 30 triterpene ginsenoside derivatives containing sugars were isolated. Yet, there is a wide variation (2–20%) in the ginsenoside content among the different ginseng species [2].

Ginseng saponins inhibit voltage-dependent  $\text{Ca}^{2+}$  channels providing one possible explanation for its analgesic efficacy because sensory neurons transfer sensory information such as pain from the peripheral nervous system toward the central nervous system [55]. Furthermore, the regulation of voltage-dependent  $\text{Ca}^{2+}$  channels by ginseng saponins is not mediated through the inhibitory receptors such as opioids,  $\alpha_2$ -adrenergic, GABAergic, nor muscarinic receptors [53].

### 3. Pharmacological mechanisms of action for naturally derived analgesic drugs

Interestingly, the identification of new compounds derived from natural sources with potential antinociceptive effect could lead to great understanding of the underlying pharmacological mechanisms of action. Herein, the next section, we will review some targeted pharmacological mechanisms of action for naturally derived analgesic drugs.

#### 3.1. Voltage-gated ion channels

Many natural products have been found to interact with voltage-gated ion channels. Some more recent natural products are to be studied at the  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Ca}^{2+}$  channels. These compounds cause their effects through several mechanisms of action.

Voltage-gated  $\text{Na}^+$  channels play a central role in the generation and dissemination of action potentials in neurons and other cells such as skeletal muscle and cardiac cells. Modulators of sodium channels are being used as local anaesthetics, antiarrhythmics, analgesics and antiepileptics, and for other disorders [56]. In this aspect, tetrodotoxin, isolated from the puffer fish, blocks sodium channels and causes great harm to those that ingest it leading to numbness in the lip and tongue within 20 min of ingestion followed by paralysis and may cause death. Consequently, the use of tetrodotoxin as a key compound for analgesic development has been limited by its toxic nature [3].

As well, voltage-gated  $\text{K}^+$  channels have been shown to be involved in pain processes. Activation of potassium channels leads to membrane hyperpolarization then inhibition of cell excitability. Those pain signals may be transmitted either directly or indirectly depending on the location of these channels. Today, several anaesthetics are used clinically to work through interactions with potassium channels [57]. Certain peptides from natural sources have been identified to act through potassium channels. For instance, tertiapin, a peptide with 21 amino acids, isolated from the venom of the honey bee, has been shown

to block inward rectifier potassium channels [58]. Moreover, administration of tertiapin in mice diminished the analgesic response evoked by spinal administration of high doses of morphine [59]. Further research in this area may result in better understanding of the pain modulation responses, managing drug addiction, and may lead to the discovery of new analgesic compounds.

Furthermore, voltage-gated  $\text{Ca}^{2+}$  channel activation directly affects membrane potential and contributes to the electrical excitability of neurons. Voltage-gated  $\text{Ca}^{2+}$  channels have an important role in the release of neurotransmitter from the presynaptic terminals in the dorsal horn in response to inward action potentials [60]. In this aspect, a peptide termed *N*-agatoxin isolated from the venom of the funnel web spider, and an American spider *Agelenopsis aperta* inhibits P/Q-type calcium channels that have been reported to play a role in migraine and headaches [61, 62]. Future research on the functional role of P/Q-type calcium channels may provide an additional target for the modulation of pain responses.

### 3.2. Acetylcholine receptors

Two classes of acetylcholine receptors are well-known, the muscarinic and the nicotinic acetylcholine receptors. Both classes were recognized through the utilization of the natural products, muscarine and nicotine, respectively. The role of these receptors in modulating the central nociception has been well-documented. The muscarinic acetylcholine receptors have several known natural product ligands including: hyoscyamine, atropine, scopolamine and Mamba snake toxins [3].

Epibatidin, an alkaloid isolated from the skin of the Ecuadorian dart-frog, *Epipedobates tricolor*, has been reported to be a potent nicotinic analgesic. It could be antagonized by mecamylamine, a nicotinic receptor antagonist [63]. Accordingly, it was established that epibatidine as a powerful tool for studying nicotinic pathways involved in pain perception. As well, its remarkable efficiency as an antinociceptive may be due to the selective effects on central antinociceptive pathways [64].

### 3.3. Cannabinoid receptors

Two cannabinoid receptors, CB1 and CB2, have been identified and subsequently cloned. They belong to G-protein coupled receptors family, sharing 44% amino acid sequence homology but vary in their anatomical distribution. Expression of CB1 receptor is mainly in the CNS and to a lesser extent in other tissues, while CB2 receptor is primarily expressed in peripheral tissues associated with immune functions, including macrophages, B and T cells, as well as in peripheral nerve terminals and on mast cells [65].

The endogenous family of ligands that interact with these receptors is known as the anandamides (*N*-arachidonoyl-ethanolamine). They are lipid in nature with antinociceptive activity but not as potent as tetrahydrocannabinol (THC) [66]. Interestingly, neurons in the brain produce, release and inactivate anandamide, confirming a role for this arachidonate derivative as an endogenous cannabinoid substance [67].

Remarkably, a nonnitrogenous lipophilic molecule,  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC), isolated from *Cannabis sativa*, is the prototypical ligand, interacting with the cannabinoid G-protein coupled receptors [68]. It has also been reported that another constituent cannabidiol isolated from *C. sativa* exerts important anti-inflammatory activity. Cannabinoid receptor agonists induce a number of unwanted CNS effects, which are supposed to be mediated mainly by the central distribution pattern of CB1 receptors [65].

### 3.4. Vanilloid receptors

Vanilloid receptors (VR), or vanilloid-gated ion channels, also known as capsaicin receptors, have been shown to be involved in nociception [69]. Nonetheless, their clinical potential remains to be proven. Vanilloid receptors are expressed almost exclusively by primary sensory neurons involved in nociception and neurogenic inflammation.

It is well established that the VR agonists give rise to excitatory effects characterized by nociception and neurogenic inflammation, followed by desensitization [14, 70]. Notably, many natural products are known as modulators of these receptors. Capsaicin, for example, is a VR1 receptor agonist and is marketed in the United States in topical preparations for the treatment of arthritis and inflammatory joint pain. At the present time, it is believed that VR1 receptor agonists can be good attractive therapeutic target. Interestingly, other “hot” spices, like piperine and zingerone, the active ingredients in black pepper and ginger, respectively, also appear to act through VR activation [71].

Peripheral fibres are the site of release of a variety of neuropeptides among which substance P (SP) and calcitonin gene-related peptide (CGRP) are defined. Depletion of SP and CGRP as well as of vanilloid receptors occurred following treatment with capsaicin, in the spinal and peripheral terminals of capsaicin sensitive neurons in almost 24 h [28].

Other naturally occurring compound acting at VR1 receptors is of fungal origin, a triprenyl phenol, termed scutigeral, a novel structural class of VR ligand. Scutigeral, isolated from the non-pungent edible mushroom *Albatrellus ovinus*, has been shown to stimulate rat dorsal root ganglion neurons by activation of vanilloid receptors [72].

### 3.5. Purinergic P2X receptors inhibitors

One pharmacological target in the area of analgesics and anti-inflammatory agents is purinergic P2X receptors (P2XR), which are important receptors in the modulation of inflammation and pain. In 1978, Burnstock [73] mentioned the existence of two classes of purinergic receptors, known as receptors P1 (adenosine) and P2 (adenosine 5'-triphosphate, ATP) [50]. Markedly, mammalian ATP-gated nonselective cation channels (P2XRs) consist of seven potential subunits; denoted P2X1 to P2X7 [74].

In 1995, a significant advance was made when the P2X3 ionotropic ion channel purinergic receptor was cloned and presented to be mainly localized on small nociceptive sensory neurons in dorsal root ganglia (DRG) [75]. Shortly, Burnstock [76] suggested a unifying purinergic

hypothesis for the initiation of pain that ATP released as a co-transmitter with noradrenaline (NA) and neuropeptide Y from sympathetic nerve terminal varicosities probably that is involved in activating these receptors in three different pain conditions: as a co-transmitter from sympathetic nerves in sympathetic pain as causalgia and reflex sympathetic dystrophy; from endothelial cells in vascular pain, including migraine and angina; and from tumour cells in cancer.

Likewise, purinergic mechano-sensory transduction has been implicated for visceral pain. Meanwhile, ATP released from urothelial cells and epithelial cells lining intestine during the distension acts on P2X3 and P2X2/3, and perhaps P2Y, receptors on subepithelial sensory nerve fibres to initiate impulses in sensory pathways to the pain centres in the brain as well as triggering local reflexes. Besides, P1, P2X and P2Y receptors are possibly implicated in nociceptive neural pathways in the spinal cord, while P2X4 receptors on the spinal microglia are involved in allodynia [77].

Of the seven subtypes of P2XR, the types that are most related to the progression or control of pain status are the P2X3R, the heteromeric P2X2/3R, P2X4R, and the P2X7R [78].

An example of natural inhibitor of purinergic receptors is a product known as puerarin. Puerarin is an isoflavone isolated from a traditional Chinese herb (*Radix puerariae*). It was found to have an inhibitory effect on burn pain hyperalgesia through inhibiting the upregulation of the P2X3R protein expression in the dorsal root ganglion neurons [79].

Also, purotoxin, a peptide isolated from the venom of the Asian spider *Geolycosp*, also showed a potent and selective antagonist effect on P2X3R, inhibiting the ionic current in rat neurons and showing an analgesic effect on inflammatory pain [78].

## 4. Conclusion

Natural products are an extremely valuable source of novel compounds with potential analgesic properties. More research needs to be conducted on natural products to discover new compounds, and hereafter, new mechanisms of actions will be elucidated.

Lastly, the fields of pharmacognosy, medicinal chemistry and pharmacology are expected to work closely to ensure that novel naturally driven compounds are explored for their potential development as novel drugs as well as their pharmacological mechanisms of action.

## Author details

Rehab Fawzy Abdel-Rahman

Address all correspondence to: rehabs2001@yahoo.com

Department of Pharmacology, National Research Centre, Giza, Egypt

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## Footnotes

Chemical structures that cite in the current chapter are taken from those provided on submitted PubChem chemical compound records, as follows:

- **Aconitine**: National Center for Biotechnology Information. PubChem Compound Database; CID=2012, <https://pubchem.ncbi.nlm.nih.gov/compound/2012>.
- **Aspirin**: National Center for Biotechnology Information. PubChem Compound Database; CID=2244, <https://pubchem.ncbi.nlm.nih.gov/compound/2244>.
- **Caffeine**: National Center for Biotechnology Information. PubChem Compound Database; CID=2519, <https://pubchem.ncbi.nlm.nih.gov/compound/2519>.
- **Capsaicin**: National Center for Biotechnology Information. PubChem Compound Database; CID=1548943, <https://pubchem.ncbi.nlm.nih.gov/compound/1548943>.
- **Codeine**: National Center for Biotechnology Information. PubChem Compound Database; CID=5284371, <https://pubchem.ncbi.nlm.nih.gov/compound/5284371>.
- **Drimanial**: National Center for Biotechnology Information. PubChem Compound Database; CID=636975, <https://pubchem.ncbi.nlm.nih.gov/compound/636975>.

- **Ginsenosides:** National Center for Biotechnology Information. PubChem Compound Database; CID=9852086, <https://pubchem.ncbi.nlm.nih.gov/compound/9852086>.
- **Lappaconitine:** National Center for Biotechnology Information. PubChem Compound Database; CID=115161, <https://pubchem.ncbi.nlm.nih.gov/compound/115161>.
- **Menthol:** National Center for Biotechnology Information. PubChem Compound Database; CID=16666, <https://pubchem.ncbi.nlm.nih.gov/compound/16666>.
- **Mitragynine hydroxyindolenine:** National Center for Biotechnology Information. PubChem Compound Database; CID=44301524, <https://pubchem.ncbi.nlm.nih.gov/compound/44301524>.
- **Mitragynine:** National Center for Biotechnology Information. PubChem Compound Database; CID=3034396, <https://pubchem.ncbi.nlm.nih.gov/compound/3034396>.
- **Morphine:** National Center for Biotechnology Information. PubChem Compound Database; CID=5288826, <https://pubchem.ncbi.nlm.nih.gov/compound/5288826>.
- **Nalorphine:** National Center for Biotechnology Information. PubChem Compound Database; CID=5284595, <https://pubchem.ncbi.nlm.nih.gov/compound/5284595>.
- **Naloxone:** National Center for Biotechnology Information. PubChem Compound Database; CID=5284596, <https://pubchem.ncbi.nlm.nih.gov/compound/5284596>.
- **Polygodial:** National Center for Biotechnology Information. PubChem Compound Database; CID=72503, <https://pubchem.ncbi.nlm.nih.gov/compound/72503>.
- **Salvinorin A:** National Center for Biotechnology Information. PubChem Compound Database; CID=128563, <https://pubchem.ncbi.nlm.nih.gov/compound/128563>.
- **Thebaine:** National Center for Biotechnology Information. PubChem Compound Database; CID=5324289, <https://pubchem.ncbi.nlm.nih.gov/compound/5324289>.
- **Theobromine:** National Center for Biotechnology Information. PubChem Compound Database; CID=5429, <https://pubchem.ncbi.nlm.nih.gov/compound/5429>.

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