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REVIEW

Recent development in antihyperalgesic effect of phytochemicals: anti-inflammatory and neuro-modulatory actions

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Abstract

Introduction Pain is an unpleasant sensation triggered by noxious stimulation. It is one of the most prevalent conditions, limiting productivity and diminishing quality of life. Non steroidal anti inflammatory drugs (NSAIDs) are widely used as pain relievers in present day practice as pain is mostly initiated due to inflammation. However, due to potentially serious side effects, long term use of these antihyperalgesic drugs raises concern. Therefore there is a demand to search novel medicines with least side effects. Herbal products have been used for centuries to reduce pain and inflammation, and phytochemicals are known to cause fewer side effects. However, identification of active phytochemicals of herbal medicines and clear understanding of the molecular mechanism of their action is needed for clinical acceptance.

Materials and methods In this review, we have briefly discussed the cellular and molecular changes during hyperalgesia via inflammatory mediators and neuro-modulatory action involved therein. The review includes 54 recently reported phytochemicals with antihyperalgesic action, as per the literature available with PubMed, Google Scholar and Scopus.

Conclusion Compounds of high interest as potential antihyperalgesic agents are: curcumin, resveratrol, capsaicin, quercetin, eugenol, naringenin and epigallocatechin gallate (EGCG). Current knowledge about molecular targets of pain and their regulation by these phytochemicals is elaborated and the scope of further research is discussed.

Keywords Nociceptor · Hypersensitivity · Nociceptive receptors · Inflammation · Herbal medicine

Introduction

The ability to respond to noxious stimuli is vital for survival of an organism and can be considered as a protective mechanism against any damage due to that particular noxious stimulus. However, this response is associated with an unpleasant distressing feeling or pain. Pain is defined by the International Association for the Study of Pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. It is evoked as a defense mechanism against noxious stimuli which warns and instructs the individual to withdraw from damaging situations, to protect a damaged body part while it heals, and to avoid similar experiences in the future [1].

Perception of pain in response to noxious simulation is initiated with triggering of specialized peripheral sensory neurons known as nociceptors. Stimulated nociceptors are hyper sensitized to a mild painful stimulus giving perception of exaggerated pain or hyperalgesia. Hyperalgesia is defined as an augmented response to a noxious stimulus which manifests as an increased sensitivity to pain [2]. As the threshold for response also decreases, sometimes even innocuous stimuli may cause pain, a phenomenon called allodynia. Hyperalgesia is a hallmark of inflammatory pain triggered in response to different types of tissue insults.

The unpleasant feeling of pain is a terrible fear for mankind, even more than death itself. Therefore, relief from pain is a primary duty of a physician. Tremendous growth in pain therapy has improved the quality of life; however, selection of perfect pain relievers is still a challenge. Targeting inflammatory mediators by non steroidal anti inflammatory

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drugs (NSAIDs) is one of the strategies applied for treatment. However, partial success of NSAIDs guided the investigators to adopt new strategy, i.e. targeting multiple mediators and pathways simultaneously. Interestingly, most of the phytochemicals show multimode action, therefore fit better in contemporary idea. Further, long-term use of traditional drugs is dangerous due to their severe side effects [3]. In general, phytochemicals show lesser side effects, which further strengthens the idea of pain treatment using phytochemicals. Therefore, a large number of phytochemicals have been tested for their antihyperalgesic potential. Most recently used antihyperalgesic phytochemicals and their molecular mechanism are reviewed.

Nociceptive signaling

Nociceptors are afferent sensory neurons present in peripheral as well as visceral regions of the organism, and are activated by noxious stimulus. Nociceptors are unique neurons with pseudo-unipolar morphology. They have a cell body located in dorsal root ganglia (DRG) with a peripheral axon and terminal (ending) that responds to the stimulus, and a axonal branch originating from cell body is bifurcated and that transmits information to the central region (spinal cord dorsal horn or its trigeminal homologue) as well as the peripheral region. Nociceptors exhibit bidirectional signaling while transmitting noxious stimuli from the periphery to the spinal cord. The two branches are indistinguishable biochemically as most of the proteins synthesized by the cell body in DRG or trigeminal ganglion are distributed to both central and peripheral terminals [4]. This unique property contributes to hypersensitization of nociceptors (Fig. 1).

Nociceptive mediators of inflammatory soup stimulate and sensitize nociceptors via various receptors present at its peripheral terminal. The noxious stimuli are propagated as electrical impulses along the peripheral and central axon of the nociceptor upto the CNS (the spinal cord for the body and the trigeminal nucleus for the head). Environmental stimuli like heat, cold, and mechanical stimuli are responded by peripheral terminal, whereas endogenous stimuli like pH, lipids, and neurotransmitters trigger both the peripheral and central terminals [5]. Many of these molecules are targets for therapeutic intervention in clinical pain conditions. Both terminals are approached in pain targeting via spinal (intrathecal) delivery or via topical application of drugs.

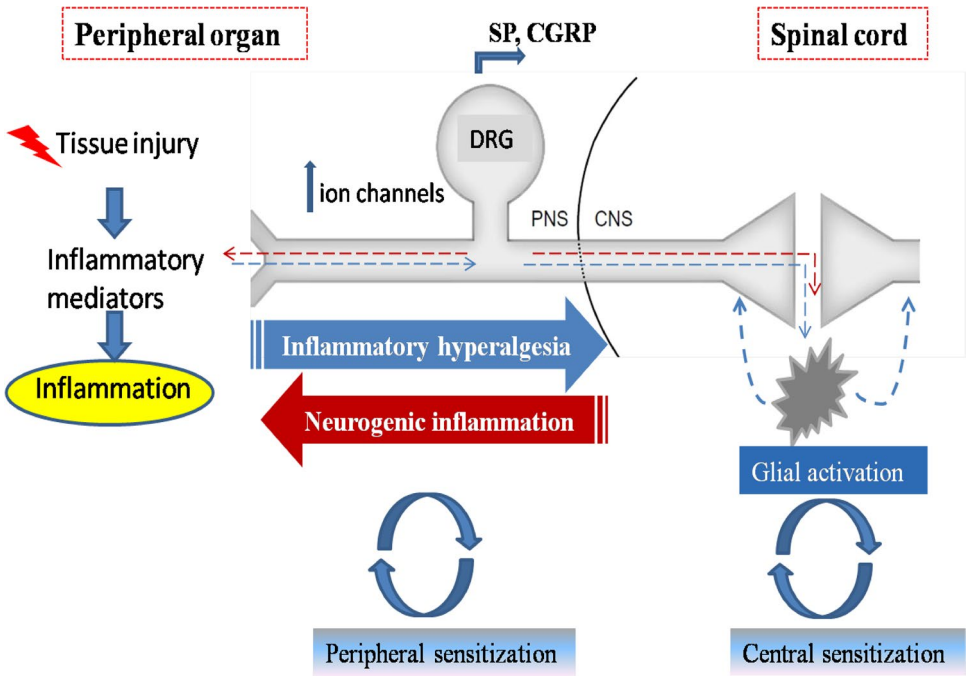

Fig. 1 Activation of nociceptors by inflammatory mediators. Inflammatory mediators are released during tissue injury, leading to activation of several ion channels which results in depolarization of nociceptive neurons. The depolarized nociceptors up regulate the expression and secretion of inflammatory neuropeptides like SP and CGRP by DRG. These neuropeptides are distributed to both ends of nociceptors through peptidergic fibers (dotted arrows show transport of inflammatory mediators). Antidromic transport of neuropeptides to peripheral site further helps in sustained inflammation. On the other hand, transported inflammatory mediators reaching dorsal horn of spinal cord stimulate post synaptic spinal neurons as well as neighboring glial cells. Inflammatory mediators act as messengers to develop a cross talk between neurons and glial cells, immunocompetent cells, sympathetic terminals, etc. which leads to hypersensitivity of dorsal horn neuron

Inflammatory mediators

Inflammatory mediators are released at peripheral site during tissue injury which may act via the surface receptors of nociceptors or by internalization, and in turn lead to activation of several ion channels resulting in depolarization of nociceptive neurons. This phenomenon is called inflammatory hyperalgesia. The depolarized nociceptors up-regulate the expression and secretion of inflammatory neuropeptides like substance-P (SP) and calcitonin gene-related peptide (CGRP) by DRG. These neuropeptides are distributed to both ends of nociceptors through peptidergic fibers. Antidromic transport of neuropeptides to peripheral site further helps in sustained inflammation. This phenomenon is called neurogenic inflammation [5]. On the other hand, transported inflammatory mediators reaching dorsal horn of spinal cord stimulate post synaptic spinal neurons as well as neighboring glial cells. Inflammatory mediators act as messengers to develop a cross talk between neurons and glial cells, immunocompetent cells, sympathetic terminals, etc. which leads to hypersensitivity of dorsal horn neurons [6].

Tissue damage or injury is accompanied by concomitant release of inflammatory mediators from local resident cells (endothelial cells, keratinocytes, and fibroblasts), infiltrated cells (neutrophils, mast cells, basophils, platelets, macrophages,) and from activated nociceptors. These mediators collectively constitute the inflammatory soup, which consists of wide range of signaling molecules including eicosinoids, cytokines, chemokines, neuropeptides, neurotrophins, as well as extracellular proteases and protons [5]. These pro-inflammatory agents act through the cell surface receptors expressed on nociceptors and initiate various signaling pathways leading to excitability and hypersensitivity of nociceptors. These inflammatory mediators are targets for development of pain relievers.

Pro-inflammatory cytokines

Pain modulation by pro-inflammatory cytokines has been studied in several animal models showing that tumor necrosis factor-alpha (TNF-α), interleukin (IL-1β and IL-6) induce and maintain hyperalgesia. Injury of peripheral nervous tissue leads to a rapid and sustained increase in cytokine secretion leading to pain behavior [7, 8].

Tumor necrosis factor-α (TNF-α)

Inflammatory cytokine TNF-α is known to play a well-established key role in several pain models [8–12]. TNF-α modulates both inflammatory and neuropathic hyperalgesia by initiating a cascade of inflammatory cytokines; therefore, its inhibitors show significant anti-hyperalgesic effects [13–15]. TNF-α receptors are expressed in both neurons and glial cells. TNF-α acts on different signaling pathways through cell surface receptors TNFR1 and TNFR2 to activate stress-activated protein kinases (SAPKs) and nuclear factor kappa B (NF-kB) during inflammation, which further activate cascade of other cytokines, notably IL-1β, IL-6, and IL-8 in the inflammatory models of carrageenan-induced and zymosan-induced hyperalgesic rats [16]. TNF-α activates tetrodotoxin-resistant voltage-gated sodium channels (TTX-r Na^+ channels) via p38 MAPK pathway in cultured DRG cells [17]. Literature suggests that TNF-α mediates central mechanisms of neuropathic pain through glial systems [18]. In response to nerve injury and inflammation, microglia secrete pro-inflammatory cytokines including TNF-α [19], which mediate its effects via the p38-MAPK pathway [20]. TNF-α auto-stimulates its own production via G-protein coupled receptor (CXCR4) and TNF-α converting enzyme [21, 22].

Despite the significant role of TNF-α in neuropathic as well as inflammatory pain, the failure of TNF-α antagonists in clinical trials has guided research towards a collective role for glia-derived different mediators and their signaling pathways in the modulation of hyperalgesia [23, 24].

Interleukin-1β (IL -1β)

IL-1β is primarily released by monocytes, macrophages, fibroblasts, and endothelial cells during cell injury and inflammation. It is also reported to be expressed in nociceptive DRG neurons and spinal cord [25]. It is known to play a key role in several pain models [7, 10, 11, 26]. IL-1β signals through complex signaling cascades that lead to the release of other nociceptive molecules such as PGE2, IL-6, SP, and MMP9 in a number of neuronal and glial cells [27, 28]. Additionally, IL-1β has been shown to cause an increase in the heat-evoked release of CGRP from rat cutaneous nociceptors in vitro [29]. RT-PCR and *in situ* hybridization studies have demonstrated expression of IL-1R1 in sensory neurons [30], which suggests that IL-1β may directly act on nociceptors. Administration of IL-1ra is reported to reduce complete Freund's

adjuvant-induced (CFA-induced) upregulation of nerve growth factor (NGF), a neurotrophic factor known to play a crucial role in a variety of acute and chronic pain states [31]. Upregulation of NGF by IL-1β is known at both the transcriptional and post-transcriptional levels [32]. IL-1β is known to modulate neuronal excitability by affecting neuronal receptors such as transient receptor potential cation channel subfamily V member 1 (TRPV1), sodium channels, gamma-aminobutyric acid (GABA) receptors, and N-methyl-D-aspartate (NMDA) receptors [33].

Interleukin-6 (IL-6)

IL-6 contributes to the development of inflammatory and neuropathic pain after a peripheral nerve injury [8, 34] and in pathogenesis of rheumatoid arthritis [35]. IL-6 is secreted by activated microglia and astrocytes, and regulates neuropeptide expression in neurons [36]. In addition, intrathecal injection of IL-6 induces tactile allodynia and thermal hyperalgesia in intact and nerve-injured rats [34].

Prostaglandin PGE2 up-regulates expression of IL-6 via EP4 receptor, and activates PKC pathway in injured nerves in case of neuropathic pain model [37]. The role of PGE2 is also demonstrated in the synthesis of IL-6 in primary sensory neurons following nerve injury. In vitro studies suggest that prostaglandin E2 receptor 4 (EP4 receptor), PKA, PKC, ERK/MAPK, CREB, and NF-kB signaling pathways are involved in PGE2-induced IL-6 production in DRG neurons [38]. IL-6 mainly activates the JAK/STAT transduction pathway in microglia of spinal cord during neuropathic pain [39]. There is evidence of IL-6 induced microglial CX3C-chemokine receptor 1 (CX3CR1) expression in the spinal cord through p38 MAPK activation after peripheral nerve injury [40].

Inflammatory enzymes

The inflammatory enzymes COX and NOS, especially their inducible isozymes COX-2 and iNOS, are implicated in the development of hyperalgesia. There are important and complex interactions between these two mediator systems.

Cyclooxygenase (COX)

COX plays a key role in biosynthesis of prostaglandins from arachidonic acid. Prostaglandins have implication in promoting inflammation and hyperalgesia. Pro-inflammatory cytokines like TNF-α induce the expression of COX in cultured DRG neurons [41]. The inducible isozyme COX-2 is expressed in inflammatory cells and tissues after inflammation and causes hyperalgesia [42]; consequently, COX-2 selective inhibitors are potent antihyperalgesic agents. COX-2 specific inhibitor coxibs markedly reduce pain symptoms in rat models of carrageenan, zymosan or formalin-evoked hyperalgesia [43–45]. COX-2 plays an important role in central sensitization after peripheral inflammation in the mouse and rat models of inflammation [46, 47]. Recent findings show the activation of both COX-1 and COX-2 in DRG during inflammatory hyperalgesia leading to activation of TRPV1 ion channels as well as PKCε [48].

Nitric oxide synthase (NOS)

NO synthesized by nitric oxide synthase (NOS) has role in spinal nociceptive processing. Over activation of different isoforms of NOS plays important role in hyperalgesia by mediating neuronal excito-toxicity by activating the receptors and downstream MAPK signaling pathways [49]. iNOS is expressed in immune cells including glial cells and is involved in several signaling pathways of hyperalgesia [50]. Pro-inflammatory cytokines like TNF-α, IL-1β, and interferon-γ induce the expression of iNOS in microglia by activation of NF-κB causing peroxynitrite injury in peripheral nerve which plays a major role in peripheral nerve dysfunction and degeneration [51].

Nociceptive receptors

In response to inflammatory mediators, nociceptors are sensitized via a number of receptors present at peripheral terminals, e.g. TRPV, voltage-dependent and transient receptor potential ankyrin (TRPA), melastatin-related transient receptor potential (TRPM), acid-sensing ion channels (ASIC), GPCR, RTK, etc. At the central level, nociceptive pathways are modulated mainly by *N*-methyl-D-aspartate receptor (NMDAR), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), neurokinin 1 receptor (NK1R), and metabotropic glutamate receptors (mGluRs). Recent studies suggest a key role of NMDAR in central sensitization during chronic pain states. Therefore, blockers of many of these ion channels are being tested for their therapeutic potential by many investigators [51–55].

The molecular transducer TRPV1 is activated by noxious heat, reduced pH, and the chemical capsaicin, whereas TRPM8, TRPV2 channels respond to cold and methanol [56] and the pungent ingredients of mustard and garlic activate TRPA1 [57]. Triggering of mechanical pain involves TRPA1 receptors and potassium channel subfamily K (KCNK) channels [5].

Several ion channels are responsible for thermal and mechanical pain hypersensitivity; out of them TRPV1 is most studied. It is an ionotropic, Ca^{2+} permeable, non-selective cation channel which is suggested to be a key target of inflammatory mediators during generation of thermal hyperalgesia [58]. Studies have shown that TRPV1 functions as an integrator of multiple signals and its sensitivity for thermal stimuli can be greatly altered by several components of the inflammatory soup [59]. Few inflammatory mediators function as direct modulators of the channel, whereas others act through downstream signaling pathways. These interactions result in a decrease in activation threshold of these ion channels resulting in allodynia and hyperalgesia. However, there is a controversy regarding the intracellular signaling mechanisms which are most effective in TRPV1 modulation [60]. Nonetheless, TRPV1 modulation is suggested to be an important phenomenon in generation of pain hypersensitivity, particularly in the setting of tissue injury-evoked inflammation. Therefore, it may act as a therapeutic target in infections, osteoarthritis or rheumatoid arthritis, and inflammatory bowel disease.

Inflammatory pathways involved in initiation and maintenance of hyperalgesia

Nuclear factor kappa B (NF-kB) pathway

Nuclear factor-κB (NF-κB) belongs to the family of inducible transcription factors, which is known to regulate a variety of genes involved in different inflammatory and immune responses such as infection, tissue injury or ROS generation [61] via production of inflammatory cytokines [62]. Under normal conditions, NF-kB is localized in the cytoplasm of the cell and remains associated with inhibitory protein inhibitor of kB (IkB); but depending upon the type of stimulus, the activation of NF-κB follows two different signaling pathways. First, the canonical NF-κB pathway is known to be triggered by proinflammatory cytokines such as TNF-α and IL-1, members of TNF receptor super family, and T-cell receptor (TCR) and B-cell receptor [63]. The signaling pathway is initiated by IKK-mediated inducible degradation of IκB; and subsequent release and translocation of NF-kB into nucleus initiates transcription of inflammatory genes like TNFα, IL-1β, which further regulate down-stream mediators [64]. Second, the non-canonical NF-κB pathway or 'alternative NF-kB pathway' is activated selectively by specific stimuli which include ligands of a subset of TNFR super family members such as Lymphotoxin β Receptor (LTβR), B-cell activating factor receptor (BAFFR), CD40 and Receptor Activator of Nuclear Factor κ B (RANK) [65]. The activation of non-canonical NF-κB pathway does not involve

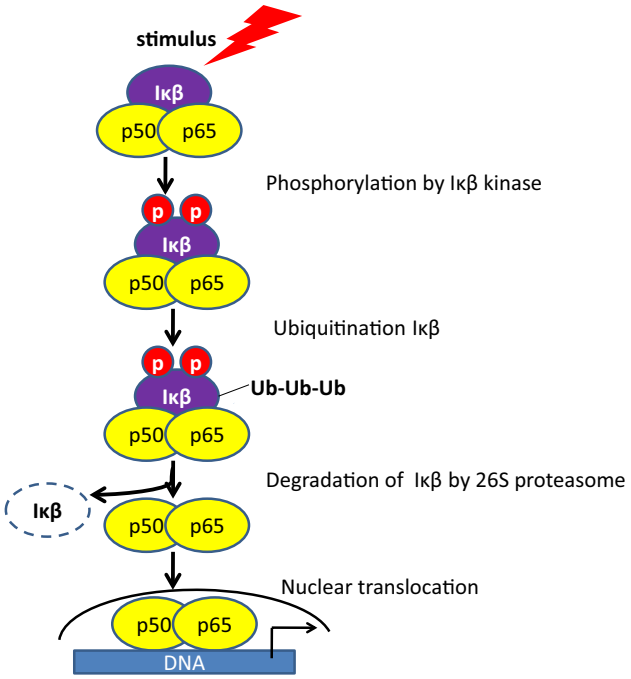

Fig. 2 Activation of NFκB pathway. NF-κB commonly refers to a p50-p65 heterodimer, which represents the major Rel/NF-κB complex in most cells. In basal conditions NF-κB is sequestered in the cytoplasm by inhibitor proteins, usually IκB. Upon stimulation, IκBα is rapidly phosphorylated by the IkB kinase complex (IKK). Phosphorylated IκB is substrate for ubiquitination and subsequent degradation by the 26S proteasome. The released NF-κB dimer is translocated to the nucleus leading to activation of target genes

IκBα degradation; rather it involves inducible phosphorylation of NF-κB2 precursor protein, p100 by IKKα leading to activation of RelB/p52 heterodimers [66]. Both the canonical and non-canonical pathways are involved in regulation of immune and inflammatory responses despite the differences in signaling mechanism [66, 67]. The activation of transcription factor NF-κB during hyperalgesia generally follows the canonical pathway [68] (Fig. 2).

NF-κB is widely recognized as a master switch that is essential for immune responses. Increased NF-κB activity in immune and nervous system cells is linked to several chronic pain conditions in humans like rheumatoid arthritis, migraine, nerve injury; as well as inflammation- and nerve injury-evoked pain in animals [69]. While NF-κB is ubiquitously expressed in a variety of cell types, its contribution is driven largely by signaling in the dorsal root ganglia and in astrocytes of spinal cord during inflammatory and neuropathic pain [70]. The activation of NF-κB in astrocytes may produce pain by decreasing the expression of catechol-o-methyltransferase (COMT), an enzyme that inactivates catecholamines and modulates pain [71]. Astrocytic NF-κB is reported to be upregulated in CFA-induced inflammation [72] as well as in nerve injury [70]. Likewise,

loss of astrocytic NF-κB signaling attenuates pain following formalin administration [73].

NSAIDs are now believed to target both the NF-kB and COX pathways, to inhibit leukocyte recruitment [74]. Recent research indicates that natural compounds reduce the inflammation and hyperalgesia by blocking the activation of NF-kB and other inflammatory mediators.

MAPK pathways

Other than the classical role of MAPKs in cell death and survival, studies in the past decade revealed direct or indirect involvement of all the three MAPKs in neuropathic and inflammatory hyperalgesia. Role of MAPKs has been suggested to be specific in pain hypersensitivity with negligible effect on physiological pain perception [75]. Various inflammatory mediators are implicated in peripheral sensitization of nociceptors and initiation of hyperalgesia. However at central site, microglia and astrocytes contribute to the release of multiple inflammatory mediators, neuromodulators, and growth factors which enhance excitability within the dorsal horn of the spinal cord [76]. Central sensitization results from activation of different membrane receptors and channels via phosphorylation, leading to various intracellular kinase cascades. Several different intracellular signal transduction cascades converge on MAPK. Peripheral or spinal nerve injury activates p38 in spinal neurons, microglia, and Astrocytes, whereas ERK activity is reported to increase in microglia and Astrocytes [77]. Recent literature suggests a significant role of p38 in post-operative pain [78]. Increasing body of evidence indicates a crucial role of glial cells in the pathogenesis of pain [79].

ERK-MAPK activation is suggested as a master switch or gate for the regulation of central sensitization [80]. Activation of ERK is reported to be induced in spinal cord dorsal horn (SCDH) neurons by persistent noxious input, produced by various sources [81]. Stimulation of DRG neurons with TNF-α leads to ERK activation, and subsequent increase in expression of TRPV1 [82]; which is a major target of peripheral sensitization. Further, morphine-induced hyperalgesia involves activation of ERK in brain cortex [83]. Recent study reveals the role of ERK signaling in the periphery as it influences the transition from acute to chronic postoperative pain [84]. Therefore, activation of ERK has been considered as neuronal marker of pain [85]. Pharmacological intervention targeted specifically at the signal transduction pathways in nociceptive neurons may provide new therapeutic opportunities for pathological pain.

Recently, we have demonstrated that ROS produced during peripheral inflammation leads to activation of ERK in DRG as well as in spinal dorsal horn [86]. Therefore, we have suggested that antihyperalgesic property of natural polyphenols like resveratrol and curcumin may be attributed to their antioxidant property [87–89]. We have shown a functional correlation between down-regulation of ERK signaling in spinal cord by resveratrol with its antioxidant and antihyperalgesic potential [89]. The findings suggest that ERK-MAPK might be a major target of natural compounds used for hyperalgesia treatment.

Antihyperalgesic drugs

Clinical and molecular studies provide evidences that inflammation is responsible for acute inflammatory hyperalgesia as well as for maintenance of chronic pain. NSAIDs are most widely used antihyperalgesic drugs, especially in case of acute hyperalgesia although their long use leads to adverse effects like risk of elevated blood pressure, blood clots, platelet dysfunction, peptic ulcer, nephropathy and renal failure, inhibition of labor, cardiac failure, and sudden cardiac death [90, 91]. Opioids are used in case of chronic hyperalgesia. The major concern of long-term treatment of opioids includes increased risk of addiction, tolerance, and neuropsychological effects. The symptoms are nausea, vomiting, constipation, itching, dizziness, sweating, sedation, lethargy, CNS adverse events, and overdose leading to death [92]. Serious side effects of available antihyperalgesic or pain relieving drugs pose a challenge to scientist to search an alternative therapy with least side effects.

Antihyperalgesic phytochemicals

Recent studies show involvement of ROS in initiation and maintenance of hyperalgesia [93]. These are implicated in inflammatory as well as neuropathic pain [94, 95]. ROS is known to mediate development and maintenance of capsaicin-induced hyperalgesia in mice, primarily through central sensitization [96]. Recently, antioxidants have shown promising effect in elimination of pain. Polyphenols of dietary source like vegetables, fruits, and drinks (wine and tea) are being tested for their analgesic action [87, 88]. Scientists are engaged in search of antioxidant and anti inflammatory agent as pain relievers with minimum side effects.

A number of herbal products with antioxidant and anti inflammatory properties are known since ancient times which exhibit anti hyperalgesic potential. These products are used to treat pain and inflammation with almost no side effects. Although safe in most cases, ancient pain therapy using herbal medicines are ignored because neither their active components nor their molecular targets are well defined. However in the past decade, scientists have identified a number of targets which are manipulated by herbal products during intervening hyperalgesia. The active

Table 1 Herbal compunds and their molecular targets during antihyperalgesic action in different pain models

Sr. no.	Herbal compound	Model of hyperalgesia	Molecular targets	References
1	Curcumin	Diabetic neuropathic pain	NO and TNF-α	[97–99]
			TRPV1	[100]
			Opioid system	[101]
			NOX	[102]
			TTX-R Na^+ channel	[103]
		Neuropathic pain	p-ERK, p-CREB	[104, 105]
			CX3CR1, NF-κB	[106]
			Monoamine system and opioid receptors	[107]
			BDNF and COX-2	[108]
			P2X3 receptor	[109]
		Inflammatory hyperalgesia	TNF-α, IL-1β and IL-6	[87]
			Nrf-2 and NF-κB	[110]
			ASICs	[111]
			TRPV1	[112]
		Morphine tolerance	Opioid receptors	[107]
		Opioid induced hyperalgesia	CaMKIIα	[113]
2	Resveratrol	Neuropathic pain	TNF-α, IL-1β, IL-6 and IL-10	[114]
			NMDAR	[115]
			SIRT1	[116, 117]
			Serotonergic system	[118]
			P2X7receptor	[119]
		Bone cancer pain	CX3CR1	[120]
		Inflammatory hyperalgesia	COX-2	[87, 121]
			COX-1	[122]
			Prostaglandin E2, COX-2	[121]
			TNF-α, IL-1β, IL-6 and IL-10	[88, 114]
			TRP channels	[123–125, 142]
			TRPA1	[126]
			Na^+ and K^+ ion channels	[124, 127]
			ERK-MAPK	[87]
			ERK and mTOR signaling	[128]
			P2×7 receptor	[129]
3	Quercetin	Inflammatory hyperalgesia	IL-1β, GSH	[130]
		Neuropathic pain	TNF-α, IL-1β, TAK1, IKK and JNK2	[131]
			c-Fos, iNOS	[132]
			Nitric oxide (NO), oxidative stress	[133]
			TLR signaling	[131]
			PKCε	[134]
		Intense acute swimming-induced muscle pain	TNF-α, IL-1β and IL-10, COX-2 NF-κB, Nrf2 and HO-1	[135]
		Tamoxifeninduced adenomyosis	TRPV1, pp38 and pERK	[136]
		Cancer pain	Oxidative stress, IL-1β and TNFα	[137]
		Rheumatoid arthritis	Glutathion(GSH), TNF-α, IL-1β, COX-2, NF-κB, Nrf-2 and HO-1	[138]
			VEGF, bFGF, MMP-2	[139]

Table 1 (continued)

Sr. no.	Herbal compound	Model of hyperalgesia	Molecular targets	References
4	Eugenol	Inflammatory hyperalgesia	TRPV1	[140]
			Voltage-gated potassium channels	[141]
		Neuropathic pain	cyclic nucleotide-gated (HCN) channels	[142]
			TTX-resistant and TTX-sensitive Na + channels	[143]
		Dental pain	Voltage-gated sodium channel	[144, 145]
5	Naringenin	Neuropathic pain	–	[146]
		Inflammatory hyperalgesia	IL-33, TNF-α, and IL-1β and NF-κB pathway	[147]
			Cytokines, Nrf-2 and the NO-cGMP-PKG-KATP Channel Signaling Pathway	[148]
		Diabetic neuropathy	Superoxide dismutase NO, TNF-α	[149, 150]
6	Epigallocatechin gallate (EGCG)	Diabetic neuropathy	Spinal ROS	[151]
		Neuropathic pain	TLR-4, TNF-α, and IL-1β and NF-κB pathway	[152]
			nNOS	[153]
			RhoA, FASN and TNF-α	[154]
			CX3CL1 Chemokine	[155]
7	Capsaicin	Neuropathic pain	TRPV1 activation	[156]
			–	[157]
			Piezo 1 and Piezo 2 activity	[158, 159]
		Inflammatory hyperalgesia	p38 MAPK/MK2/PGE2 Axis	[160]
8	p-Cymene	Inflammatory hyperalgesia	Opioid system and cytokines	[161]
9	Citronellol	Inflammatory hyperalgesia	–	[162]
10	Carvacrol	Inflammatory hyperalgesia	–	[163]
		Cancer pain	IL-10 and GABAA	[164]
11	Trans-caryophyllene	Inflammatory and Neuropathic pain	IL-1β, opioid and endocannabinoid system	[165]
12	α-spinasterol	Inflammatory hyperalgesia	TRPV1	[166]
13	Lycopene	Neuropathic pain	Connexin 43	[167]
			Oxidative stress markers and antioxidant system	[168]
		Diabetic neuropathy	–	[169]
14	Tingenone	Inflammatory hyperalgesia	Opioidergic system	[170]
			NO/cGMP and ATP-sensitive K(+) channels	[171]
15	Ellagic acid	6-hydroxidopamine induced hyperalgesia	–	[172]
16	6-Gingerol	Neuropathic pain	–	[173]
17	Emodin	Neuropathic pain	P2X2/3 receptor	[174]
		–	TRPV1	[175]
18	Fisetin	Diabetic neuropathy	ROS, spinal GABAA receptors	[176]
		Neuropathic pain	Spinal serotonergic system	[177]
19	Reutin	Inflammatory hyperalgesia	Opioidergic system	[178]
20	Baicalin	Neuropathic pain	HDAC1	[179]
21	Genistein	Neuropathic pain	Proinflammatory cytokines, NGF, iNOS and eNOS	[180]
22	Diosmin	Neuropathic pain	IL-1β, Tnfα, and IL-33/St2	[181]
		Acetic acid-induced visceral pain	IL-6, IL-1β, and TNF-α, opioid and D_2 dopaminergic pathways	[182]

Table 1 (continued)

Sr. no.	Herbal compound	Model of hyperalgesia	Molecular targets	References
23	Myricitrin	Chemical models of overt nociception	Nitric oxide-L-arginine and protein kinase C pathways	[183]
		Postoperative pain	–	[184]
24	Vitexin	Postoperative pain	Opioid receptors and GABAA receptors	[185]
		Inflammatory hyperalgesia	TRPV1, oxidative stress, and cytokines	[186]
25	Hesperidin	Neuropathic pain	TNF-α and IL-1β, oxido-nitrosative stress	[187]
			TNF-α, IL-1β and IL-6	[188]
26	Luteolin	Neuropathic pain	GABAA receptors	[189]
27	Puerarin	Neuropathic pain	IL-6, IL-1β, and TNF-α and NF-κB pathway	[190]
28	Liquiritigenin	Neuropathic pain	–	[191]
29	Hesperetin	Neuropathic pain	IL-6, IL-1β, and TNF-α, oxidative stress	[192]
30	Cardamonin	Inflammatory hyperalgesia	COX-2 and Tgase-2	[193]
			TNF-α, IL-1β, and IL-6	[194]
		Neuropathic pain	Opioidergic system	[195]
		–	hTRPA1 Cation Channel	[196]
31	Morin	Bone cancer pain	TNF-α, IL-1β, and IL-6, IL-10	[197]
32	Tanshinone IIA	Neuropathic pain	TNF-α, IL-1β and MAPK pathways	[198]
		Inflammatory hyperalgesia	IL1-β, IL-6, TNF-α and NF-κB pathway, TRPV1	[199]
		Bone cancer pain	IL-1β, IL-6 and TNF-α	[200]
33	(+)-Borneol	Inflammatory and Neuropathic pain	–	[201]
		Neuropathic pain	TRPA1	[202]
34	Citral	Inflammatory hyperalgesia	Serotonin	[203]
35	Celastrol	Inflammatory and Neuropathic pain	Cannabinoid pathway	[204]
36	Parthenolide	Neuropathic pain	NF-κB, p38MAPK, ERK1/2, IL-1β, IL-18, iNOS, IL-6, IL-10, and TIMP1	[205]
37	Euphol	Inflammatory and Neuropathic pain	–	[206]
38	Maslinic acid	Inflammatory hyperalgesia		[207]
39	Lupeol	Inflammatory and post operative pain	IL-1β and TNF-α	[208]
40	Bilobalide	Inflammatory hyperalgesia	–	[209]
41	Linalool	Acute pain	–	[210]
42	Zerumbone	Neuropathic pain	–	[211]
			Arginine-nitric oxide-cGMP-K^+ ATP channel	[212]
			5-HT receptors	[213]
43	Sinularin	Inflammatory hyperalgesia	iNOS, COX-2 and TGF-β	[214]
44	Bullatine A	Neuropathic pain, inflammatory pain, diabetic neuropathic pain,and bone cancer pain	microglial dynorphin A	[215]
45	Lemnalol	Neuropathic pain	TNF-α	[216]
46	Salvinorin A	Inflammatory hyperalgesia	kappa opioid receptor and CB1 receptor	[217]
47	Incarvillateine	Inflammatory and Neuropathic pain	Adenosine system	[218]
48	Ursolic acid	Neuropathic pain	pro-inflammatory cytokines and oxidative stress	[219]
		Inflammatory hyperalgesia	PPARα	[220]
49	Retinoic acid	Inflammatory hyperalgesia	PPAR-β/δ receptors	[221]
50	Carnosol and carnosic acid	–	microsomal prostaglandin E_2 synthase-1 (mPGES-1) and 5-lipoxygenase (5-LO)	[222]
51	Garcinol	Neuropathic pain	(IL)-1β, IL-6, iNOS, COX-2, NF-κB	[223]
52	Ginsenoside Rg3	Incision pain	IL-1β and IL-6	[224]

Table 1 (continued)

Sr. no.	Herbal compound	Model of hyperalgesia	Molecular targets	References
53	Carnosic acid	Neuropathic pain	sirtuin1 and p66shc	[225]
54	Paeoniflorin	Chemotherapy induced pain	adenosine A1 receptors	[226]

components are shown to inhibit the activation, release, and action of inflammatory mediators.

Here, we have reviewed more than 50 antihyperalgesic phytochemicals used in the studies conducted recently (Table 1). Three sources were used to search for appropriate papers. These included Medline-PubMed, Google Scholar, and Scopus using different combinations of keywords like pain, hyperalgesia, phytochemicals, herbal products, and phytotherapy. The databases were searched for studies published after 2010. Citations were limited to purified active constituents. Studies using crude or partially purified plant extracts were excluded. Additional papers were included by searching name of individual phytochemical in combination with above key words; and after the analysis of all references from the selected articles (some of them were published before 2010). Seven most cited phytochemicals; Curcumin, capsaicin, resveratrol, quercetin, eugenol, naringenin, and EGCG have been described in detail.

Curcumin

In India and other parts of Asia, turmeric is used to treat many health conditions. Curcumin, a substance in turmeric, may help to reduce inflammation. Both the ancient Indian and Chinese systems of medicine have recognized curcumin's beneficial properties for thousands of years. Curcumin is considered as an excellent pain reliever [227–230]. It is believed to have anti-inflammatory, antioxidant, and anticancer properties [231–233]. Several studies suggest that it might ameliorate pain and inflammation in animal models and in case of human osteoarthritis and rheumatoid arthritis [234]. We have shown antihyperalgesic action of curcumin in rodents by modulation of antioxidant enzymes and down regulation of TNF-α, IL-1β and IL-6 [87]. Curcumin attenuates diabetic neuropathic pain in mouse, possibly through its inhibitory action on NO and TNF-α release [97, 98]. Curcumin has been shown to regulate numerous transcription factors [106, 110], cytokines [99], protein kinases [104, 105], adhesion molecules, redox status [87] and enzymes [102] that have been linked to hyperalgesia. It can inhibit the activity and the synthesis of COX-2 and 5-lipooxygenase (5-LOX), as well as other enzymes that have been implicated in inflammation and hyperalgesia [102, 108]. Curcumin is shown to be as effective as ibuprofen for the treatment of knee osteoarthritis with fewer gastrointestinal adverse effects [235]. It is believed to lead to a phase out of NSAID use, at least as a treatment for mild-to-moderate osteoarthritis. Now modern research is showing that curcumin may be one of nature's most powerful potential healers.

Curcumin contains vanilloid ring similar to that present in capsaicin, the main pungent ingredient in hot chili peppers (Fig. 3). The burning sensation of chili pepper is mediated via activation of capsaicin receptor (TRPV1). Recent studies demonstrate that pain relieving action of curcumin is due to antagonism of TRPV1 [100, 112]. In addition, antihyperalgesic action of curcumin is mediated by inhibition of other ion channels like TTXR-Na + channel and ASICs [103, 111]. Curcumin-induced antinociceptive action on neuropathic pain has also been reported via inhibition of TNF-α/NO release [97, 99], as well as by differential regulation of descending monoamine system and opioid receptors [101, 107, 113].

In spite of tremendous potential of curcumin in pain relief, its use is generally limited by its poor bioavailability. Therefore, research has been focused to increase its bioavailability by nano-encapsulation [109, 236, 237]. Nano-encapsulated curcumin shows better bioavailability

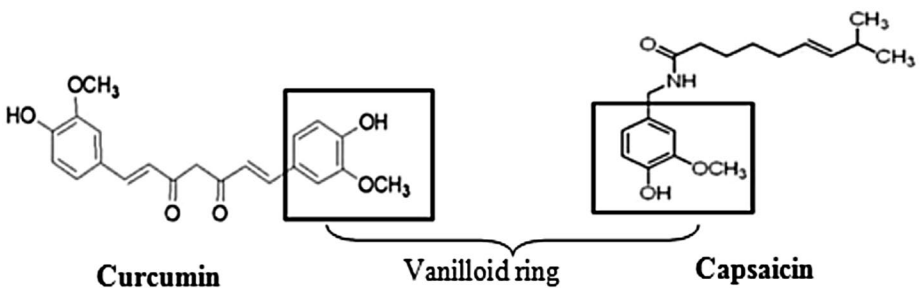

Fig. 3 Structural similarity between curcumin and capsaicin

and relieve pain by inhibiting brain-derived neurotrophic factor (BDNF) and P2X purinoceptor 3 (P2X3) [109, 237].

Capsaicin

Capsaicin is the main pungent ingredient in hot chili peppers has been used as a topical analgesic for centuries. Capsaicin is a highly selective agonist for TRPV1 receptors expressed in afferent neuronal C fibers and some Aδ fibers. Prolonged activation of TRPV1 by capsaicin through enzymatic or osmotic changes results in loss of receptor functionality, causing impaired local nociception for extended periods [156]. Capsaicin-induced local depletion of substance P was previously thought to be its mechanism for pain relief. However, this is no longer considered to be the case, rather other mechanisms may be involved [157]. For instance, Borbiro et al (2015) have demonstrated that activation of TRPV1 inhibits Piezo channels through a calcium-induced depletion of phosphoinositides [158]. This regulation could contribute to the cellular mechanisms by which the TRPV1 activation by capsaicin mitigates mechanical hypersensitivity. Recently capsaicin is demonstrated to alleviate inflammation by targeting MAPK-PGE2 pathway which has broadened our understanding for new avenues of therapy in neuro-inflammatory pain [160].

Resveratrol

Resveratrol is a natural polyphenol and a phytoalexin produced by several plants in response to injury or when the plant is under attack by pathogens such as bacteria or fungi (Fig. 4). Sources of resveratrol in food include the skin of grapes, blueberries, raspberries, mulberries. Richest sources of resveratrol are grapes and red wine. It has no known toxic side-effects [238]. The anti-inflammatory activity of resveratrol has been well documented and can be ascribed to inhibition of pro-inflammatory cytokines, chemokines and promotion of anti-inflammatory cytokine IL-10 [88, 114, 120]. It is reported to suppress the nociceptive neuronal activity [239, 240]. Resveratrol could be a complementary and alternative medicine to clinical pain management approaches, especially in patients with chronic severe pain being treated with morphine for long time through action on the NMDA receptors and neuroinflammatory responses [115, 241, 242].

Previous reports indicate anti-nociceptive action of resveratrol by inhibition of COX-1 and COX-2 activity during inflammation-induced hyperalgesia [121, 122]. But now it is almost established that resveratrol decreases the production of prostaglandin E2 (PGE2) by inhibiting the cyclooxygenase (COX)-2 cascades [121]. Inhibitory action of resveratrol on spinal COX-2 expression has also been demonstrated in our lab [87].

In addition to anti-inflammatory mechanism, anti-hyperalgesic action of resveratrol is also supported by modulation of the activity of voltage'-gated and ligand-gated ion channels at peripheral and central levels. Resveratrol has been reported to modulate the excitability of neurons in the peripheral nervous system by activating voltage-dependent and transient receptor potential (TRP) channels [123–126]. Inhibition of TRP ankyrin 1 (TRPA1), a mechano-sensitive channel by resveratrol [126], suggests that it inhibits action potential firing via the mechanical transduction process. Moreover, Na^+ and K^+ ion channels of DRG are also modulated by resveratrol [124, 127]. Furthermore, antinociceptive effect of resveratrol after systemic administration appears to be mediated via an opioidergic mechanism [243]. Interestingly, opioidergic and inflammatory pathways are linked with concomitant ROS generation [244]. ROS is now considered as an essential component of hyperalgesia development. Therefore, anti-oxidant property of resveratrol is supposed to a key property which might be employed in most of its anti-hyperalgesic mechanisms [245, 246]. In this context, we recently analyzed the effect of resveratrol treatment on modulation of endogenous antioxidant defense system in peripheral and central nervous system. We found a correlation between modulation of antioxidant enzymes and anti-hyperalgesic effect of resveratrol. Furthermore, ROS scavenging property of resveratrol was also manifested in

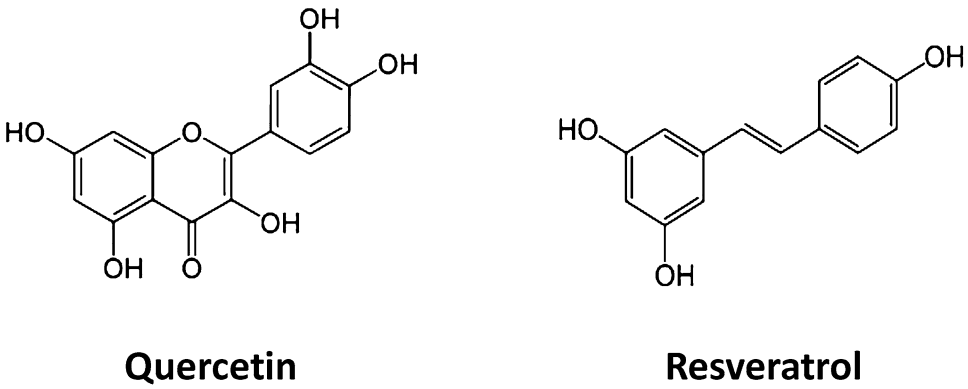

Fig. 4 Structure of resveratrol and quercetin

modulation of ROS sensitive signaling pathway such as TNFR1-ERK signaling [89]. ERK activation in spinal dorsal horn is now considered as hallmark of hyperalgesia which serves as a single convergence point for several signaling pathways; therefore, inhibition of ERK signaling in spinal cord further strengthens the candidature of resveratrol as a potent anti-hyperalgesic agent [85]. Resveratrol potently inhibits IL-6-mediated signaling to ERK in sensory neurons, blocking the perception of pain. Resveratrol administered at the time of incision is capable of completely blocking the development of persistent pain sensitization by upregulating the N-methyl-D-aspartate receptor (NMDAR) which is thought to be significant in morphine tolerance. Blocking NMDAR function effectively weakens tolerance to morphine and increases morphine's analgesic properties [115]. Inhibition of microglial activation via AMPK signaling by resveratrol further contributes to reduce morphine's tolerance [128, 247]. Other targets of resveratrol during hyperalgesia are P2X purinoceptor 7 (P2X7) and Sirtuin 1 (Sirt1) [116, 117, 119, 129]. Recent reports suggest its antihyperalgesic action by inhibiting glial activation [248].

Quercetin

Quercetin, a plant polyphenol is one of the most abundant dietary flavonoids, found in many fruits, vegetables, leaves, and grains (Fig. 4). Quercetin is classified as an antioxidant and is reported to exhibit a wide range of pharmacological properties, for example, anti-inflammatory and anticancerous [249], anti-hepatic fibrosis [250], anti-hyperalgesic [131], and neuroprotective in different animal models of neuropathy [132, 133, 251].

Quercetin is a non-specific protein kinase enzyme inhibitor [252]. The analgesic effects of quercetin observed in models of nociception were described to be dependent on many mechanisms, including NO production, activation of GABA and serotonin receptors, opioid like effects, inhibition of TRPV1 and NMDAR, inhibition of inflammatory cytokines (TNF-α and IL-1β) and inflammatory enzyme (COX-2) as well as by reducing oxidative stress [130, 253]. Quercetin is reported to elucidate its neuroprotective effect in diabetic neuropathy [251], alcohol-induced neuropathy [133], arthritic pain [138, 139, 254–256], adenomyosis-induced hyperalgesia [136], cancer-evoked pain [137] and paclitaxel-induced nuropathic pain [134]. Quercetin is a potential molecule for the treatment of muscle pain conditions. It reduces muscle mechanical hyperalgesia by inhibiting myeloperoxidase (MPO) and NAG activities, cytokine production, oxidative stress, COX-2 and NFκB activation; and by inducing Nrf2 and HO-1 and glial cells' activation [135, 257]. Recently, Nie *et al*. (2017) have reported that quercetin decreases hyperalgesia by decreasing the expression levels of TRPV1, pp38, and pERK in DRG neurons suggesting that potential mechanism of action of quercetin is through reduced central sensitization [136].

Eugenol

Eugenol is a colorless to pale yellow, aromatic oily liquid extracted from certain essential oils especially from clove oil (80–95%), nutmeg, cinnamon, basil, and bay leaf. Eugenol

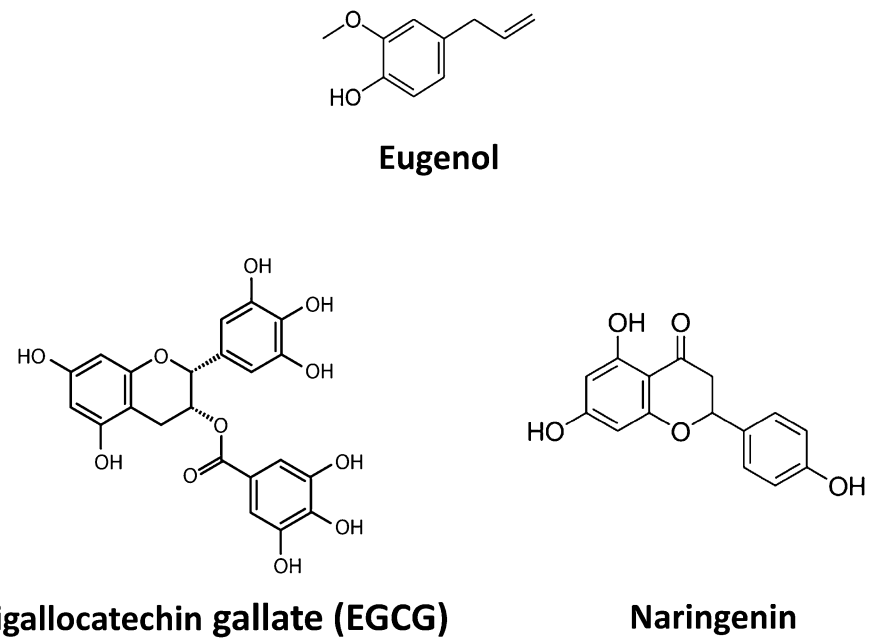

Fig. 5 Structure of eugenol, EGCG, and naringenin

(4-allyl-2-methoxyphenol) a methoxyphenol with a short hydrocarbon chain is a member of the phenylpropanoids class of chemical compounds (Fig. 5).

Pharmacologic studies have demonstrated that eugenol has anticonvulsant [258], local anesthetic [259], antistress [260], and anti-oxidation activity because of its ability to reduce superoxide to H_2O_2 [261] or to scavenge the free radicals through chelation of metal ions [262]. It shows anti-bacterial [263], antifungal [140], and anti-inflammatory activity by inhibiting inflammatory mediators such as COX-2, IL-1β, and TNF-α in LPS-activated macrophages and analgesic activity due to selective binding at the capsaicin receptor [264]. In pre-clinical studies, eugenol shows its antihyperalgesic action in neuropathic and arthritic hyperalgesia [142, 265, 266]. Eugenol is used as a local anesthetic. Reversible inhibition of nerve impulse and compound action potentials by eugenol was recorded in various nerves including tooth pulp nerve, sciatic nerve, and superior cervical ganglion neurons of rats [267]. It has been extensively used as a therapeutic agent in dentistry for sedation in patients with toothache, pulpitis, and dental hyperalgesia.

Eugenol successfully inhibited voltage-gated sodium channels when tested in dental primary afferent neurons [144] and DRG neurons [145] of rats, suggesting that eugenol might block action potentials in both nociceptive afferent fibers. Supporting evidence is yet to be found whether eugenol binds directly to voltage-gated sodium channels and modulate; however, it is clear that modulation of voltage-gated sodium channels is a mechanism that contributes to the analgesic action of eugenol. Voltage-gated potassium channels play roles in repolarization of cell membrane after action potential firing. Eugenol has been found to inhibit voltage-gated potassium channels in both capsaicin-sensitive and capsaicin-insensitive neurons [141]. Eugenol exerts its anesthetic action via antagonism of NMDAR, an NMDA-sensitive ionotropic glutamate receptor [268] that plays an important role in synaptic modulation and memory function.

Naringenin

Naringenin is a bitter and colorless flavonoid, predominantly found in grapefruit (Fig. 5). It has shown several biological activities like antioxidant, anti-inflammatory, anti-cancerous, and neuroprotective effects in several studies. Likewise, its antihyperalgesic potential has been revealed during past 5 years. Till date, its antihyperalgesic potential could be attributed to its antioxidant property. The anti-hyperalgesic potential of naringenin in diabetic neuropathy is shown by modulation of oxidative and inflammatory markers [149] and by improvement in the activity of antioxidant enzyme superoxide dismutase (SOD) [150]. Further studies revealed its effect on ROS-dependant downstream signaling pathways in inflammatory hyperalgesia. Recently, naringenin has been demonstrated to show its effect on superoxide anion-induced as well as CFA-induced hyperalgesia via modulation of oxidative stress, cytokines, nuclear factor erythroid 2-related factor 2 (Nrf-2), and NO – cGMP – PKG pathway [147, 148]. Furthermore, naringenin treatment is also effective in neuropathic pain by inhibition of microglial activation in spinal cord [146]. However, use of naringenin as antihyperalgesic agent is limited due to its poor bioavailability. Attempts should be made to increase its bioavailability either by structural modification or by nano-conjugation in order to attain final development.

Epigallocatechin gallate (EGCG)

Epigallocatechin gallate (EGCG), also known as epigallocatechin-3-gallate, is the most abundant catechin in tea, found in high content in the dried leaves of green tea (Fig. 5). It is a polyphenol which has recently attracted several scientists across the globe due to its tremendous potential to affect human health and disease. EGCG is known to have neuroprotective effects in various pathological states in the nervous system [269], which is generally attributed to its antioxidant property. Initial studies have shown that its antioxidant property may also be exploited for relief in neuropathic pain. The antihyperalgesic action of EGCG is suggested to be brought by inhibition of spinal nNOS which has encouraged researchers to exploit the antioxidant property of EGCG for relief in neuropathic patient [153]. Similarly, its potential to decrease diabetes-induced neuropathic pain is demonstrated by reduction in spinal ROS [151]. Further studies suggest the involvement of other inflammatory mediators in its antihyperalgesic action. For instance, intrathecal injection of EGCG is reported to improve the pain behaviors in CCI-induced neuropathic pain which is accompanied by decreased expression of TLR4, NF-κB, HMGB1, TNF-α, and IL-1β and increased content of IL-10 in the spinal cord [152]. Recent reports suggest a new role of EGCG during alleviation of neuropathic pain, i.e. inhibition of neuronal–microglial communication. It is attained by inhibition of chemokine CX3CL1 and RhoA expression in spinal cord [154, 155].

In general high doses of EGCG are required for treatment of neuropathic pain. Therefore, administration of pure EGCG in pills or capsule forms may be appropriate for alleviating neuropathic pain [154]. However, further research evidences are required before implementation of this mode of treatment.

Summary and future scope

A number of inflammatory mediators like pro-inflammatory cytokines TNF-α, IL -1β, IL-6, and inflammatory enzymes COX, NOS; nociceptive receptors TRPV, TRPA, TRPM, NMDAR, AMPAR, and channels ASIC, KCNK; and inflammatory pathways like NF-kB pathways and MAPK pathways provide specific molecular targets for pain therapy. We have reviewed the mechanism of action of herbal products of recent interest and the target points which are being intervened in treating inflammation and hyperalgesia.

An antihyperalgesic drug should be able to act at peripheral level or central level or at both levels simultaneously, depending upon different etiologies of different pain conditions. Therefore, pharmacognocy and pharmacokinetics of herb-derived phytochemicals is needed before therapeutical use. Another concern is the poor absorption and, therefore, low bioavailability of most of the phytochemicals. Their tissue availability may be improved by some structural modifications or by targeted nano-delivery. Furthermore, toxicological parameters must be checked in this course. The scientific development in this direction is not satisfactory. Future research should focus on pharmacokinetics, targeted nano- delivery, and toxicological parameters of phytochemicals.

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Compliance with ethical standards

Conflict of interest Authors declare that there is no conflict of interest.

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