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REVIEW ARTICLE

The Emerging Role of Quercetin in the Treatment of Chronic Pain

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Abstract: Despite much research efforts being devoted to designing alternative pharmacological interventions, chronic pain remains to be an unresolved clinical problem. Quercetin, a compound that belongs to the flavonoids family, is abundantly found in fruits and vegetables. Emerging evidence indicates that quercetin possesses anti-nociceptive effects in different rodent models of chronic pain, including inflammatory pain, neuropathic pain and cancer pain. In this review, we summarize the mechanisms underlying the analgesic effect of quercetin in preclinical studies. These studies showed that quercetin exerts potent analgesic effects against chronic pain *via* suppressing neuroinflammation and oxidative stress as well as modulation of synaptic plasticity, GABAergic system, and opioidergic system. Considering that the safety of quercetin is well established, it has great potential for clinical use in pain treatment.

Keywords: Chronic pain, quercetin, neuroinflammation, oxidative stress, synaptic plasticity, GABAergic system.

1. INTRODUCTION

Chronic pain is pain that lasts more than several months, which significantly affects an individual's quality of life [1, 2]. Currently, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids remain to be the first-line analgesics for the management of chronic pain in the clinic [3, 4]. However, long-term use of NSAIDs and opioids inevitably causes unacceptable side effects. Despite much research efforts being devoted to designing alternative pharmacological interventions, chronic pain remains to be an unresolved clinical problem [5-7]. Therefore, novel therapeutic targets and strategies are urgently needed for the management of chronic pain.

Quercetin, a compound that belongs to the flavonoids family, is abundantly found in fruits and vegetables [8, 9]. It has been reported that quercetin may play a critical role in the prevention or treatment of various diseases, such as neurological diseases and cancers [10, 11]. Emerging evidence indicates that quercetin possesses anti-nociceptive effects in different rodent models of chronic pain, including inflammatory pain, neuropathic pain, and cancer pain [12-14]. Anjaneyulu *et al.* provided the first evidence that chronic treatment with quercetin significantly attenuated streptozotocin-induced thermal hyperalgesia and cold allodynia [15]. In a rat model of chronic constriction injury (CCI)-induced neuropathic pain, Civi *et al.* showed that the analgesic effect of quercetin was significantly superior to gabapentin and morphine [13]. Moreover, administration of quercetin dose-dependently alleviated thermal hyperalgesia and mechanical allodynia in paclitaxel-induced neuropathic pain mice *via* inhibiting the expression of protein kinase C epsilon isoform and transient receptor potential vanilloid 1cation channel in the spinal cords and DRG [16]. In another study, Li *et al.* demonstrated that chronic treatment with quercetin considerably ameliorated bone cancer pain *via* suppressing peripheral and central sensitization [12]. It has been reported that the sigma-1 receptor plays a critical role in the generation and maintenance of chronic pain [17, 18]. Recently, Espinosa-Juarez *et al.* demonstrated that the sigma-1 receptor antagonist potentiated the anti-nociceptive effect of quercetin in neuropathic pain induced by CCI [19]. As its safety is well established, quercetin has great potential for clinical use in pain treatment. In this review, we summarized and discussed the preclinical evidence demonstrating the therapeutic potential of quercetin in chronic pain.

2. EFFECT OF QUERCETIN ON NEUROINFLAMMATION IN CHRONIC PAIN

Neuroinflammation is characterized by activation of glial cells such as microglia and astrocytes, overproduction of proinflammatory cytokines and chemokines, and infiltration of immune cells in the peripheral and central nervous system (CNS) [20-22]. A great deal of evidence from our laboratory and others has demonstrated that neuroinflammation plays a vital role in chronic pain [22-24]. Recent evidence indicates that quercetin exerts neuroprotective effects *via* suppression of neuroinflammation in the CNS [25-27]. In a rat model of spared nerve injury (SNI)-induced neuropathic pain, Muto *et al.* demonstrated that oral administration of quercetin attenu-

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ated mechanical allodynia *via* inhibiting the activation of satellite glial cells in the ipsilateral L5 dorsal root ganglions (DRG) [28]. In another study, Yang *et al.* showed that chronic treatment with quercetin significantly ameliorated mechanical allodynia and thermal hyperalgesia in a rat model of diabetic neuropathic pain [29]. Moreover, they found that quercetin suppressed the upregulation of the P2X4 receptor and activation of satellite glial cells as well as the upregulation of phosphorylated p38 mitogen-activated protein kinase (MAPK) in the DRG of diabetic neuropathic pain rats. Recently, Ye *et al.* reported that administration of quercetin considerably attenuated CCI-induced neuropathic pain *via* suppressing the activation of microglia in the spinal cord [30]. Taken together, these results demonstrate that quercetin exerts analgesic effects against chronic pain *via* inhibiting the activation of glial cells in DRG and spinal cord.

It is well-established that glial cell activation releases proinflammatory cytokines and chemokines, which play a critical role in the development of chronic pain [31-33]. Valerio *et al.* reported that intraperitoneal and oral treatment with quercetin dose-dependently ameliorated formalin- and carrageenan-induced inflammatory pain by suppressing the production of interleukin 1beta (IL-1β) in the paw skin [34]. Moreover, they also found that quercetin inhibited the hypernociception induced by intra-plantar injection of tumor necrosis factor α (TNF-α) and CXCL1. In a mice model of cancer pain, Calixto-Campos *et al.* showed that quercetin significantly reduced Ehrlich tumor-induced mechanical allodynia and thermal hyperalgesia *via* inhibiting the production of TNF-α and IL-1β as well as neutrophil recruitment [35]. In another study, Ji *et al.* showed that single or continuous oral administration of quercetin significantly attenuated thermal and cold hyperalgesia in spinal nerve ligation (SNL)-induced neuropathic pain [36]. Moreover, they found that quercetin administration inhibited the upregulation of TNF-α and IL-1β in the DRG from SNL rats. Furthermore, quercetin decreased the phosphorylation of transforming growth factor-β-activated kinase, inhibitor of nuclear factor-κB-kinase, and c-Jun N-terminal kinase 2 in cultured astrocytes. Palmitoylethanolamide (PEA), a naturally-occurring fatty acid amide, is well-known for its analgesic and anti-inflammatory properties [37, 38]. Britti *et al.* investigated the analgesic effect of PEA co-ultramicronized with the quercetin (PEA-Q) on carrageenan-induced inflammatory pain and sodium monoiodoacetate (MIA)-induced osteoarthritis pain [14]. They found that intragastrical (i.g.) administration of PEA-Q 30 minutes before carrageenan injection significantly improved thermal hyperalgesia and reduced activity of myeloperoxidase (MPO), a marker of inflammatory cell infiltration. Moreover, PEA-Q treatment also considerably alleviated mechanical allodynia and thermal hyperalgesia in MIA-treated rats by counteracting the increased serum levels of TNF-α, IL-1β, and nerve growth factor. These findings confirmed the analgesic and anti-inflammatory effects of the new composite PEA-Q in rodent inflammatory pain models. Moreover, Ruiz-Miyazawa *et al.* demonstrated that subcutaneous (s.c.) injection of quercetin markedly suppressed monosodium urate crystals (MSU)-induced mechanical hyperalgesia, leukocyte recruitment, activation of nuclear factor kappa B (NF-κB), and release of TNF-α and IL-1β [39]. Considering the pivotal role of the NLR family pyrin domain containing 3 (NLRP3) inflammasome-mediated neuroinflammation in chronic pain [40-42], they further determined the effect of quercetin on the activation of NLRP3 inflammasome. They found that quercetin treatment dramatically suppressed the upregulation of NLRP3, C-terminal caspase recruitment domain, and pro-caspase-1 in the knee joints after MSU injection. Their further study verified the analgesic effect of quercetin on titanium dioxide (TiO2)-induced arthritis pain [43]. In a rat model of CCI-induced neuropathic pain, Ye *et al.* reported that administration of quercetin for 21 days starting from 7 days after CCI surgery significantly improved the paw withdrawal threshold and paw withdrawal latency in response to von Frey filament stimuli in CCI rats, which was reversed by AMP-activated protein kinase (AMPK) inhibitor Compound C [30]. Moreover, they found that chronic treatment with quercetin not only reduced the inflammatory cells at the ligation site of the sciatic nerve, but also reduced the levels of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6. Furthermore, quercetin treatment inhibited the activation of mitogen-activated protein kinase (MAPK), which was reversed by AMPK inhibitor Compound C. These results demonstrated that quercetin may attenuate neuropathic pain via activation of AMPK and inhibition of MAPK signaling pathways. Taken together, these studies indicate that quercetin exerts analgesic effects against chronic pain via suppressing the release of proinflammatory cytokines and chemokines in DRG and spinal cord.

3. EFFECT OF QUERCETIN ON OXIDATIVE STRESS IN CHRONIC PAIN

Quercetin is widely used in traditional Chinese medicine due to its potent antioxidant activity [45, 45]. Valerio *et al.* reported that quercetin dose-dependently reversed the down-regulation of glutathione (GSH) in the paw skin of formalin- and carrageenan-induced inflammatory pain mice [34]. Moreover, Raygude *et al.* demonstrated that chronic treatment with quercetin for 10 weeks significantly ameliorated mechanical allodynia and thermal hyperalgesia in ethanol-induced neuropathic pain rats [46]. Additionally, quercetin treatment considerably decreased elevated levels of malondialdehyde (MDA), a biomarker of oxidative stress, and oxidative stress-induced DNA fragmentation and upregulation of nitric oxide (NO) in ethanol-treated rats. It is important to note that physiological amounts of NO are neuroprotective, while higher concentrations are obviously neurotoxic [47]. Furthermore, the preconditioning signal leading to cellular protection through hormesis is an important redox-dependent aging-associated with free radicals species accumulation, and inflammatory responses involved in cellular survival mechanisms [48, 49]. Interestingly, bilirubin, a final product of heme metabolism, can serve as an endogenous scavenger of both NO and reactive nitrogen species [50, 51]. In a mouse model of oxaliplatin-induced neuropathic pain, Azevedo *et al.* showed that quercetin significantly attenuated mechanical allodynia and thermal hyperalgesia via suppressing lipid peroxidation and protein nitrosylation in the spinal cord [52]. In another study, Calixto-Campos *et al.* showed that quercetin attenuated Ehrlich tumor-induced cancer pain by improving the antioxidant defense system as evidenced by restoration of GSH levels, free-radical scavenging ability, and ferric-reducing ability potential (FRAP) [35]. Similarly,

Ruiz-Miyazawa *et al.* demonstrated that administration of quercetin remarkably ameliorated MSU-induced mechanical hyperalgesia and improved the antioxidant defense system [39]. Moreover, quercetin inhibited the production of superoxide anions and upregulation of gp91phox after MSU injection. Their further study showed that chronic treatment with quercetin also significantly attenuated TiO2-induced mechanical hyperalgesia via similar mechanisms [43]. Previously, our laboratory has demonstrated that activation of nuclear factor erythroid-2-related factor 2 (Nrf2), a critical regulator of endogenous antioxidant defense, exerts potent analgesic effects on chronic pain [53-56]. Borghi *et al.* reported that quercetin treatment showed an analgesic effect via activation of the nuclear Nrf2/heme oxygenase-1 (HO-1) signaling pathway [43]. Taken together, quercetin may attenuate chronic pain by suppressing oxidative stress due to an improved antioxidant defense system.

4. EFFECT OF QUERCETIN ON SYNAPTIC PLASTICITY IN CHRONIC PAIN

A great deal of evidence indicates that synaptic plasticity is a key cellular mechanism for the development and maintenance of chronic pain [57, 58]. Wang *et al.* reported that administration of quercetin once daily for 8 weeks significantly alleviated thermal hyperalgesia in diabetic neuropathic pain mice [59]. Moreover, chronic quercetin treatment reduced the total dendritic length, the number of dendritic branches, and the dendritic spine density in the spinal cord dorsal horn neurons of diabetic neuropathic pain mice. Furthermore, they found that quercetin treatment inhibited the upregulation of synaptic plasticity associated proteins and the phosphorylated levels of mammalian target of rapamycin and p70 ribosomal S6 kinase in the spinal cord of diabetic neuropathic pain mice. These results indicate that quercetin alleviates diabetic neuropathic pain by inhibiting mTOR/p70S6K - mediated changes in synaptic morphology and synaptic plasticity-associated proteins in the spinal cord.

5. EFFECT OF QUERCETIN ON GABAERGIC SYSTEM IN CHRONIC PAIN

γ-aminobutyric acid (GABA) is a well-known inhibitory neurotransmitter in the CNS. Emerging evidence from our laboratory and others has demonstrated that loss of GABAergic inhibition contributes to the development and maintenance of chronic pain [33, 60-62]. Filho *et al.* demonstrated that quercetin dose-dependently ameliorated formalin- and capsaicin-induced inflammatory pain, which was significantly reversed by GABAA receptor antagonist or GABAB receptor antagonist [63]. However, the underlying mechanisms remain unclear. Nevertheless, a recent study showed that quercetin displayed good binding affinities with GABA receptor subunits such as A5, B1, and B2 [64]. Overall, these results indicate that quercetin may exert analgesic effects via restoring GABAergic inhibition.

6. EFFECT OF QUERCETIN ON THE OPIOIDERGIC SYSTEM IN CHRONIC PAIN

It is well-established that the endogenous opioid system has been implicated in chronic pain [65, 66]. In a mice model of diabetic neuropathic pain, Anjaneyulu *et al.* provided the first evidence that quercetin significantly attenuated thermal hyperalgesia, which was reversed by naloxone, an opioid receptor antagonist [67]. In another study, Calixto-Campos *et al.* reported that the analgesic effect of quercetin on Ehrlich tumor-induced cancer pain was reversed by naloxone [35]. Notably, co-administration of morphine and quercetin at doses that were ineffective as a single treatment attenuated Ehrlich tumor-induced cancer pain. Furthermore, Ruiz-Miyazawa *et al.* demonstrated that quercetin substantially attenuated MSU-induced mechanical hyperalgesia, which was blocked by pre-treatment with naloxone [39]. Moreover, the inhibitory effects of quercetin on both neuroinflammation and oxidative stress in MSU-injected mice were abolished by pre-treatment with naloxone. Taken together, these results demonstrated that quercetin possesses anti-nociceptive property, probably through modulation of the opioidergic mechanism.

CONCLUSION AND FUTURE PERSPECTIVE

In this review, we summarized and discussed the therapeutic potential of quercetin against chronic pain in preclinical studies (Table **1**). These studies showed that quercetin exerts potent analgesic effects against chronic pain via suppressing neuroinflammation and oxidative stress as well as modulation of synaptic plasticity, GABAergic system, and opioidergic system (Fig. **1**). However, these findings raise further questions.

First of all, current studies indicate that the analgesic effects of quercetin rely on mechanisms in the peripheral nervous system and spinal cord. It has been reported that quercetin showed medium permeability across the blood-brain barrier [68]. Moreover, supraspinal mechanisms are of great importance to chronic pain [69, 70]. Therefore, whether quercetin exerts analgesic effects via supraspinal mechanisms needs further exploration.

Secondly, the evidence mentioned above is based on studies mostly using male rodents, although most patients with chronic pain are women. It is becoming increasingly clear that sex difference exists in pain processing [71, 72], highlighting the necessity of including subjects of both sexes in preclinical pain research. It would be interesting to investigate whether quercetin possesses a similar analgesic effect on chronic pain in female rodents.

Additionally, it is well-established that hyperpolarization-activated cyclic-nucleotide-gated (HCN) channels play a critical role in chronic pain [73, 74]. Interestingly, Liang *et al.* demonstrated that quercetin remarkably left-shifted the voltage-dependent activation curves of HCN channels and decelerated the deactivation process [75]. These results indicate that quercetin might be a potent HCN channels blocker, which sheds light on the mechanism of the analgesic effects of quercetin.

Finally, despite the promising future of quercetin in chronic pain, few clinical trials are available. Nevertheless, it should be noted that supplementation with a mango leaf extract (Zynamite®) in combination with quercetin attenuated muscle pain caused by exercise-induced muscle damage and accelerated the recovery of muscle performance in humans.

Table 1. Summary of therapeutic potential of quercetin in chronic pain.

Model	Treatment Strategy	Effects	Mechanisms	References
Carrageenan-induced inflammatory pain rats	PEA-Q (10 and 20 mg/kg, i.g.) was administered 30 min before carrageenan injection.	PWL↑	MPO↓	[8]
Formalin-induced inflammatory pain mice Capsaicin-induced inflammatory pain mice	Quercetin (10-60 mg/kg, i.p. or 100-500 mg/kg, i.g.) was administered on 30 minutes before formalin or capsaicin injection	PWL↑	Activation of GABAergic system Activation of 5-HT receptors	[21]
Formalin-induced inflammatory pain mice Carrageenan-induced inflammatory pain mice	Quercetin (3, 10, 30 and 100 mg/kg, i.p. or 30, 100 and 300 mg/kg, i.g.) was administered on 30 minutes before formalin or capsaicin injection	PWL↑	IL-1β↓ GSH↓	[60]
MSU-induced gout arthritis pain mice	Quercetin (10, 30 and 100 mg/kg, s.c.) was administered on 30 minutes before MSU injection.	PWT↑	Activation of opioidergic system Leukocyte recruitment↓ NF-κB, TNF-α, IL-1β↓ NLRP3, ASC, pro-caspase-1↓ GSH, FRAP, ABTS↑ Superoxide anion, gp91phox↓	[53]
TiO_2-induced arthritis pain mice	Quercetin (10, 30 and 100 mg/kg, i.p.) was administered once daily for 30 days starting from the first day after TiO_2 injection.	PWT↑	Leukocyte recruitment↓ Neutrophil recruitment↓ TNF-α, IL-1β, IL-6, COX2↓ GSH, FRAP, ABTS↑ Superoxide anion, gp91phox↓ Nrf2, HO-1↑	[7]
MIA-induced osteoarthritis pain rats	PEA-Q (10 and 20 mg/kg, i.g.) was administered three times per week for 21 days starting from the third day after MIA injection.	PWT↑ PWL↑	TNF-α, IL-1β, NGF↓ MMP1, MMP3, MMP9↓	[8]
CCI-induced neuropathic pain rats	Quercetin (100 mg/kg, i.p.) was administered at 21 days after CCI surgery. Quercetin (100 mg/kg, i.p.) was administered for 4 consecutive days before CCI surgery. Quercetin (100 mg/kg, i.p.) was administered for 4 consecutive days after CCI surgery.	PWT↑ PWL↑	/	[16]
CCI-induced neuropathic pain rats	Quercetin (30, 60 and 120 mg/kg, i.g.) was administered for 21 days starting from 7 days after CCI surgery.	PWT↑ PWL↑	Microglial activation↓ p-JNK, p-p38, p-ERK↓ TNF-α, IL-6, IL-1β↓	[65]
CCI-induced neuropathic pain rats	Quercetin (5.6, 17.8, 56.2, 177.8 and 316 mg/kg, s.c.) was administered on 10 days after CCI surgery.	PWT↑ PWL↑	/	[20]
SNL-induced neuropathic pain rats	A single administration of quercetin (100 mg/kg, i.g.) was performed on 14 days after SNL surgery. Quercetin (100 mg/kg, i.g.) was administered for 14 days starting from 0 day after SNL surgery. Quercetin (100 mg/kg, i.g.) was administered for 14 days before SNL surgery.	PWL↑	TNF-α, IL-1β↓ MMP-9, MMP-2, CCL2↓ NF-κB, TAK1, JNK2↓	[33]
SNI-induced neuropathic pain rats	MF diet containing 1% or 0.1% quercetin was given from 4 days before SNI surgery until sacrifice. MF diet containing 1% quercetin was given from 7 days after SNI surgery.	PWT↑	Activation of satellite glial cells↓ p-STAT3↓	[48]
STZ-induced diabetic neuropathic pain rats	Quercetin (10 mg/kg, i.g.) was administered for 4 weeks starting from 21 days after STZ-injection.	PWL↑	/	[2]

(Table 1) contd….

Model	Treatment Strategy	Effects	Mechanisms	References
STZ-induced diabetic neuropathic pain rats	Quercetin (50 mg/kg, i.p.) was administered for 14 days starting from 7 days after STZ-injection.	PWT↑ PWL↑	Activation of satellite glial cells↓ P2X4 receptor↓ p38 MAPK↓	[64]
STZ-induced diabetic neuropathic pain mice	A single administration of quercetin (50 and 100 mg/kg, i.p.) was performed on 4 weeks after STZ injection.	PWL↑	Activation of opioidergic system	[1]
Diabetic neuropathic pain in *db/db* mice	Quercetin (50 and 100 mg/kg, i.g.) was administered once daily for 8 weeks.	PWL↑	Changes of synaptic morphology↓ PSD-95, synaptophysin↓ mTOR, p70S6K↓	[62]
Oxaliplatin-induced neuropathic pain mice	Quercetin (25, 50 and 100 mg/kg) was administered 30 minutes before every oxaliplatin injection.	PWT↑ PWL↑	MDA↓ Fos, nitrotyrosine, iNOS↓	[3]
Paclitaxel-induced neuropathic pain mice	Quercetin (20, and 60 mg/kg) was administered once daily starting from the first day after the first injection of paclitaxel for 40 days in rats. Quercetin (20, and 60 mg/kg) was administered once daily starting from the first day after the first injection of paclitaxel for 12 days in mice.	PWT↑ PWL↑	PKCε, TRPV1↓	[23]
Ethanol-induced neuropathic pain rats	Quercetin (10, 20 and 40 mg/kg, i.g.) was administered for 10 week starting from 1 hour before ethanol administration.	PWT↑ PWL↑	MDA, MPO, NO↓ DNA fragmentation↓	[51]
TCI-induced bone cancer pain mice	Quercetin (5, 10 and 20 mg/kg, i.g.) was administered once daily for 21 days starting from the first day after TCI.	PWT↑	TNF-α, IL-1β↓ RANKL, RANK, OPG↓ PAR2, TRPV1↓	[38]
Ehrlich tumor-induced cancer pain mice	Quercetin (10, 30 and 100 mg/kg, i.p.) was administered on 8 days after injection of tumor cells. Quercetin (10, 30 and 100 mg/kg, i.p.) was administered once daily for 12 days after injection of tumor cells.	PWT↑ PWL↑	Activation of opioidergic system Neutrophil recruitment↓ TNF-α, IL-1β↓ GSH, FRAP, ABTS↑	[12]

Abbreviations: ABTS: free radical scavenging ability; ASC: C-terminal caspase recruitment domain; CCI: chronic constriction injury; CCL2: C-C Motif chemokine ligand 2; COX-2: cyclooxygenase 2; DNA: deoxyribonucleic acid; ERK: extracellular regulated protein kinases; 5-HT: 5-hydroxytryptamine; FRAP: ferric reducing ability potential; GSH: glutathione; HO-1: heme oxygenase-1; IL-1β: interleukin 1beta; IL-6: interleukin 6; i.g.: intragastrically; iNOS: inducible nitric oxide synthase; i.p.: intraperitoneally; i.t.: intrathecally; JNK: c-Jun N-terminal kinase; MAPK: mitogen-activated protein kinase; MDA: malondialdehyde; MIA: monoiodoacetate; MPO: myeloperoxidase; MMP: matrix metallopeptidase; MSU: monosodium urate crystals; mTOR: mammalian target of rapamycin; NF-κB: nuclear factor kappa B; NGF: nerve growth factor; NO: nitric oxide; NLRP3: NLR family pyrin domain containing 3; Nrf2: nuclear factor erythroid-2-related factor 2; OPG: osteoprotegerin; PAR2: protease-activated receptor 2; PEA-Q: palmitoylethanolamide-quercetin; PI3K: phosphoinositide 3-kinase; PSD-95: postsynaptic density protein-95; p70S6K: 70 kDa ribosomal protein S6 kinase; PWL: paw withdrawal latency; PWT: paw withdrawal threshold; RANKL: receptor activator of nuclear factor-kappa B ligand; RANK: receptor activator of nuclear factor-kappa B; SNI: spared nerve injury; SNL: spinal nerve ligation; s.c.: subcutaneously; STAT3: signal transducer and activator of transcription 3; STZ: streptozotocin; TAK1: TGF-β activated kinase 1; TCI: tumor cell implantation; TiO_2: titanium dioxide; TNF-α: tumor necrosis factor α; TRPV1: transient receptor potential vanilloid 1; ↑: upregulated; ↓: downregulated.

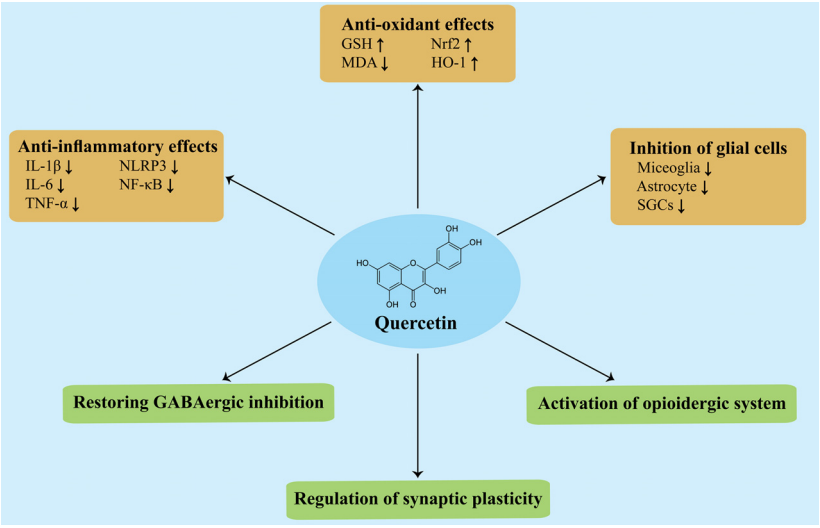

Fig. (1). The mechanisms underlying the analgesic effect of quercetin in preclinical studies. **Abbreviations:** GSH: glutathione; HO-1: heme oxygenase-1; IL-1β: interleukin 1β; IL-6: interleukin 6; MDA: malondialdehyde; NF-κB: nuclear factor kappa B; NLRP3: NLR family pyrin domain containing 3; Nrf2: nuclear factor erythroid-2-related factor 2; SGCs: satellite glial cells. TNF-α: tumor necrosis factor-α; *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

Moreover, a randomized controlled trial reported that quercetin supplementation significantly improved the clinical symptoms in women with rheumatoid arthritis, including morning pain and after-activity pain. Overall, considering that the safety of quercetin is well established, it has great potential for clinical use in pain treatment.

LIST OF ABBREVIATIONS

AMPK	=	AMP-activated protein kinase
CCI	=	Chronic constriction injury
CNS	=	Central nervous system
DRG	=	Dorsal root ganglions
FRAP	=	Ferric-reducing ability potential
GABA	=	γ-aminobutyric acid
GSH	=	Glutathione
HCN	=	Hyperpolarization-activated cyclic-nucleotide-gated
HO-1	=	Heme oxygenase-1
IL-1β	=	Interleukin 1beta
MAPK	=	Mitogen-activated protein kinase
MDA	=	Malondialdehyde
MPO	=	Myeloperoxidase
MSU	=	Monosodium urate crystals
NF-κB	=	Nuclear factor kappa B
NLRP3	=	NLR family pyrin domain containing 3
NO	=	Nitric oxide
Nrf2	=	Nuclear factor erythroid-2-related factor 2
NSAIDs	=	Nonsteroidal anti-inflammatory drugs
PEA	=	Palmitoylethanolamide
SNI	=	Spared nerve injury
SNL	=	Spinal nerve ligation
TNF-α	=	Tumor necrosis factor α
TiO2	=	Titanium dioxide

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Goldberg, D.S.; McGee, S.J. Pain as a global public health priority. *BMC Public Health,* **2011**, *11*(1), 770. http://dx.doi.org/10.1186/1471-2458-11-770 PMID: 21978149

[2] Ge, M.M.; Zhou, Y.Q.; Tian, X.B.; Manyande, A.; Tian, Y.K.; Ye, D.W.; Yang, H. Src-family protein tyrosine kinases: A promising target for treating chronic pain. *Biomed Pharmacother,* **2020**, 110017.

[3] Palop Larrea, V.; Martinez-Mir, I. Use of opioids for chronic non-cancer pain. *Med. Clin. (Barc.),* **2021**, *156*(2), 96-98. http://dx.doi.org/10.1016/j.medcli.2019.10.024 PMID: 32183985

[4] Eccleston, C.; Cooper, T.E.; Fisher, E.; Anderson, B.; Wilkinson, N.M. Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents. *Cochrane Database Syst. Rev.,* **2017**, *8*, CD012537. PMID: 28770976

[5] Sideris-Lampretsas, G.; Malcangio, M. Microglial heterogeneity in chronic pain. *Brain Behav. Immun.,* **2021**, *96*, 279-289. http://dx.doi.org/10.1016/j.bbi.2021.06.005 PMID: 34139287

[6] Culp, C.; Kim, H.K.; Abdi, S. Ketamine use for cancer and chronic pain management. *Front. Pharmacol.,* **2021**, *11*, 599721. http://dx.doi.org/10.3389/fphar.2020.599721 PMID: 33708116

[7] Zhou, Y.Q.; Liu, D.Q.; Chen, S.P.; Sun, J.; Zhou, X.R.; Xing, C.; Ye, D.W.; Tian, Y.K. The role of CXCR3 in neurological diseases. *Curr. Neuropharmacol.,* **2019**, *17*(2), 142-150. http://dx.doi.org/10.2174/1570159X15666171109161140 PMID: 29119926

[8] Zhao, L.; Wang, H.; Du, X. The therapeutic use of quercetin in ophthalmology: Recent applications. *Biomed Pharmacother,* **2021**, *137*, 111371.

[9] Soofiyani, S.R.; Hosseini, K.; Forouhandeh, H.; Ghasemnejad, T.; Tarhriz, V.; Asgharian, P.; Reiner, Ž.; Sharifi-Rad, J.; Cho, W.C. Quercetin as a novel therapeutic approach for lymphoma. *Oxid. Med. Cell. Longev.,* **2021**, *2021*, 1-15. http://dx.doi.org/10.1155/2021/3157867 PMID: 34381559

[10] Grewal, A.K.; Singh, T.G.; Sharma, D.; Sharma, V.; Singh, M.; Rahman, M.H.; Najda, A.; Walasek-Janusz, M.; Kamel, M.; Albadrani, G.M.; Akhtar, M.F.; Saleem, A.; Abdel-Daim, M.M. Mechanistic insights and perspectives involved in neuroprotective action of quercetin. *Biomed Pharmacother,* **2021**, *140*, 111729.

[11] Ghafouri-Fard, S.; Shabestari, F.A.; Vaezi, S.; Abak, A.; Shoorei, H.; Karimi, A.; Taheri, M.; Basiri, A. Emerging impact of quercetin in the treatment of prostate cancer. **2021**, *138*, 111548.

[12] Li, Z.; Zhang, J.; Ren, X.; Liu, Q.; Yang, X. The mechanism of quercetin in regulating osteoclast activation and the PAR2/TRPV1 signaling pathway in the treatment of bone cancer pain. *Int. J. Clin. Exp. Pathol.,* **2018**, *11*(11), 5149-5156. PMID: 31949595

[13] Çivi, S.; Emmez, G.; Dere, Ü.A.; Börcek, A.Ö.; Emmez, H. Effects of quercetin on chronic constriction nerve injury in an experimental rat model. *Acta Neurochir. (Wien),* **2016**, *158*(5), 959-965. http://dx.doi.org/10.1007/s00701-016-2761-0 PMID: 26960544

[14] Britti, D.; Crupi, R.; Impellizzeri, D.; Gugliandolo, E.; Fusco, R.; Schievano, C.; Morittu, V.M.; Evangelista, M.; Di Paola, R.; Cuzzocrea, S. A novel composite formulation of palmitoylethanolamide and quercetin decreases inflammation and relieves pain in inflammatory and osteoarthritic pain models. *BMC Vet. Res.,* **2017**, *13*(1), 229. http://dx.doi.org/10.1186/s12917-017-1151-z PMID: 28768536

[15] Anjaneyulu, M.; Chopra, K. Quercetin attenuates thermal hyperalgesia and cold allodynia in STZ-induced diabetic rats. *Indian J. Exp. Biol.,* **2004**, *42*(8), 766-769. PMID: 15573524

[16] Gao, W.; Zan, Y.; Wang, Z.J.; Hu, X.; Huang, F. Quercetin ameliorates paclitaxel-induced neuropathic pain by stabilizing mast cells, and subsequently blocking PKCε-dependent activation of TRPV1. *Acta Pharmacol. Sin.,* **2016**, *37*(9), 1166-1177. http://dx.doi.org/10.1038/aps.2016.58 PMID: 27498772

[17] Choi, S.R.; Han, H.J.; Beitz, A.J.; Lee, J.H. Intrathecal interleukin-1beta decreases sigma-1 receptor expression in spinal astrocytes in a murine model of neuropathic pain. *Biomed. Pharmacother*. **2021**, *144*, 112272.

[18] Ruiz-Cantero, M.C.; González-Cano, R.; Tejada, M.Á.; Santos-Caballero, M.; Perazzoli, G.; Nieto, F.R.; Cobos, E.J. Sigma-1 receptor: A drug target for the modulation of neuroimmune and neu-

roglial interactions during chronic pain. *Pharmacol. Res.,* **2021**, *163*, 105339.
http://dx.doi.org/10.1016/j.phrs.2020.105339 PMID: 33276102

[19] Espinosa-Juárez, J.V.; Jaramillo-Morales, O.A.; Déciga-Campos, M.; Moreno-Rocha, L.A.; López-Muñoz, F.J. Sigma-1 receptor antagonist (BD -1063) potentiates the antinociceptive effect of quercetin in neuropathic pain induced by chronic constriction injury. *Drug Dev. Res.,* **2021**, *82*(2), 267-277.
http://dx.doi.org/10.1002/ddr.21750 PMID: 33051885

[20] Jiang, B.C.; Liu, T.; Gao, Y.J. Chemokines in chronic pain: Cellular and molecular mechanisms and therapeutic potential. *Pharmacol. Ther.,* **2020**, *212*, 107581.
http://dx.doi.org/10.1016/j.pharmthera.2020.107581 PMID: 32450191

[21] Ji, R.R.; Nackley, A.; Huh, Y.; Terrando, N.; Maixner, W. Neuroinflammation and central sensitization in chronic and widespread pain. *Anesthesiology,* **2018**, *129*(2), 343-366.
http://dx.doi.org/10.1097/ALN.0000000000002130 PMID: 29462012

[22] Liu, D.Q.; Zhou, Y.Q.; Gao, F. Targeting cytokines for morphine tolerance: A narrative review. *Curr. Neuropharmacol.,* **2019**, *17*(4), 366-376.
http://dx.doi.org/10.2174/1570159X15666171128144441 PMID: 29189168

[23] Zhou, Y.Q.; Liu, Z.; Liu, H.Q.; Liu, D.Q.; Chen, S.P.; Ye, D.W.; Tian, Y.K. Targeting glia for bone cancer pain. *Expert Opin. Ther. Targets,* **2016**, *20*(11), 1365-1374.
http://dx.doi.org/10.1080/14728222.2016.1214716 PMID: 27428617

[24] Ji, R.R.; Xu, Z.Z.; Gao, Y.J. Emerging targets in neuroinflammation-driven chronic pain. *Nat. Rev. Drug Discov.,* **2014**, *13*(7), 533-548.
http://dx.doi.org/10.1038/nrd4334 PMID: 24948120

[25] Benameur, T.; Soleti, R.; Porro, C. The potential neuroprotective role of free and encapsulated quercetin mediated by miRNA against neurological diseases. *Nutrients,* **2021**, *13*(4), 1318.
http://dx.doi.org/10.3390/nu13041318 PMID: 33923599

[26] Olayinka, J.; Eduviere, A.; Adeoluwa, O.; Fafure, A.; Adebanjo, A.; Ozolua, R. Quercetin mitigates memory deficits in scopolamine mice model *via* protection against neuroinflammation and neurodegeneration. *Life Sci.,* **2022**, *292*, 120326.
http://dx.doi.org/10.1016/j.lfs.2022.120326 PMID: 35031260

[27] Lee, B.; Yeom, M.; Shim, I.; Lee, H.; Hahm, D.H. Protective effects of quercetin on anxiety-like symptoms and neuroinflammation induced by lipopolysaccharide in rats. *Evid Based Complement Alternat. Med.,* **2020**, *2020*, 4892415.

[28] Muto, N.; Matsuoka, Y.; Arakawa, K.; Kurita, M.; Omiya, H.; Taniguchi, A.; Kaku, R.; Morimatsu, H. Quercetin attenuates neuropathic pain in rats with spared nerve injury. *Acta Med. Okayama,* **2018**, *72*(5), 457-465.
PMID: 30369602

[29] Yang, R.; Li, L.; Yuan, H.; Liu, H.; Gong, Y.; Zou, L.; Li, S.; Wang, Z.; Shi, L.; Jia, T.; Zhao, S.; Wu, B.; Yi, Z.; Gao, Y.; Li, G.; Xu, H.; Liu, S.; Zhang, C.; Li, G.; Liang, S. Quercetin relieved diabetic neuropathic pain by inhibiting upregulated $P2X_4$ receptor in dorsal root ganglia. *J. Cell. Physiol.,* **2019**, *234*(3), 2756-2764.
http://dx.doi.org/10.1002/jcp.27091 PMID: 30145789

[30] Ye, G.; Lin, C.; Zhang, Y.; Ma, Z.; Chen, Y.; Kong, L.; Yuan, L.; Ma, T. Quercetin alleviates neuropathic pain in the rat CCI model by mediating AMPK/MAPK pathway. *J. Pain Res.,* **2021**, *14*, 1289-1301.
http://dx.doi.org/10.2147/JPR.S298727 PMID: 34040433

[31] Zhou, Y.Q.; Liu, Z.; Liu, Z.H.; Chen, S.P.; Li, M.; Shahveranov, A.; Ye, D.W.; Tian, Y.K. Interleukin-6: An emerging regulator of pathological pain. *J. Neuroinflammation,* **2016**, *13*(1), 141.
http://dx.doi.org/10.1186/s12974-016-0607-6 PMID: 27267059

[32] Zhou, Y.Q.; Gao, H.Y.; Guan, X.H.; Yuan, X.; Fang, G.G.; Chen, Y.; Ye, D.W. Chemokines and their receptors: Potential therapeutic targets for bone cancer pain. *Curr. Pharm. Des.,* **2015**, *21*(34), 5029-5033.
http://dx.doi.org/10.2174/1381612821666150831141931 PMID: 26320755

[33] Ge, M.M.; Chen, S.P.; Zhou, Y.Q.; Li, Z.; Tian, X.B.; Gao, F.; Manyande, A.; Tian, Y.K.; Yang, H. The therapeutic potential of GABA in neuron-glia interactions of cancer-induced bone pain. *Eur. J. Pharmacol.,* **2019**, *858*, 172475.
http://dx.doi.org/10.1016/j.ejphar.2019.172475 PMID: 31228456

[34] Valério, D.A.; Georgetti, S.R.; Magro, D.A.; Casagrande, R.; Cunha, T.M.; Vicentini, F.T.M.C.; Vieira, S.M.; Fonseca, M.J.V.; Ferreira, S.H.; Cunha, F.Q.; Verri, W.A., Jr Quercetin reduces inflammatory pain: Inhibition of oxidative stress and cytokine production. *J. Nat. Prod.,* **2009**, *72*(11), 1975-1979.
http://dx.doi.org/10.1021/np900259y PMID: 19899776

[35] Calixto-Campos, C.; Corrêa, M.P.; Carvalho, T.T.; Zarpelon, A.C.; Hohmann, M.S.N.; Rossaneis, A.C.; Coelho-Silva, L.; Pavanelli, W.R.; Pinge-Filho, P.; Crespigio, J.; Bernardy, C.C.F.; Casagrande, R.; Verri, W.A., Jr Quercetin reduces Ehrlich tumor-induced cancer pain in mice. *Anal. Cell. Pathol. (Amst.),* **2015**, *2015*, 1-18.
http://dx.doi.org/10.1155/2015/285708 PMID: 26351625

[36] Ji, C.; Xu, Y.; Han, F.; Sun, D.; Zhang, H.; Li, X.; Yao, X.; Wang, H. Quercetin alleviates thermal and cold hyperalgesia in a rat neuropathic pain model by inhibiting Toll-like receptor signaling. **2017**, *94*, 652-658.

[37] D'Amico, R.; Impellizzeri, D.; Cuzzocrea, S.; Di Paola, R. ALI-Amides update: Palmitoylethanolamide and its formulations on management of peripheral neuropathic pain. *Int. J. Mol. Sci.,* **2020**, *21*(15), 5330.
http://dx.doi.org/10.3390/ijms21155330 PMID: 32727084

[38] Mabou Tagne, A.; Fotio, Y.; Lin, L.; Squire, E.; Ahmed, F.; Rashid, T.I.; Karimian Azari, E.; Piomelli, D. Palmitoylethanolamide and hemp oil extract exert synergistic anti-nociceptive effects in mouse models of acute and chronic pain. *Pharmacol. Res.,* **2021**, *167*, 105545.
http://dx.doi.org/10.1016/j.phrs.2021.105545 PMID: 33722712

[39] Ruiz-Miyazawa, K.W.; Staurengo-Ferrari, L.; Mizokami, S.S.; Domiciano, T.P.; Vicentini, F.T.M.C.; Camilios-Neto, D.; Pavanelli, W.R.; Pinge-Filho, P.; Amaral, F.A.; Teixeira, M.M.; Casagrande, R.; Verri, W.A., Jr Quercetin inhibits gout arthritis in mice: Induction of an opioid-dependent regulation of inflammasome. *Inflammopharmacology,* **2017**, *25*(5), 555-570.
http://dx.doi.org/10.1007/s10787-017-0356-x PMID: 28508104

[40] Wang, H.; Huang, M.; Wang, W.; Zhang, Y.; Ma, X.; Luo, L.; Xu, X.; Xu, L.; Shi, H.; Xu, Y.; Wang, A.; Xu, T. Microglial TLR4-induced TAK1 phosphorylation and NLRP3 activation mediates neuroinflammation and contributes to chronic morphine-induced antinociceptive tolerance. *Pharmacol. Res.,* **2021**, *165*, 105482.
http://dx.doi.org/10.1016/j.phrs.2021.105482 PMID: 33549727

[41] Chen, R.; Yin, C.; Fang, J.; Liu, B. The NLRP3 inflammasome: An emerging therapeutic target for chronic pain. *J. Neuroinflammation,* **2021**, *18*(1), 84.
http://dx.doi.org/10.1186/s12974-021-02131-0 PMID: 33785039

[42] Chen, S.P.; Zhou, Y.Q.; Wang, X.M.; Sun, J.; Cao, F.; HaiSam, S.; Ye, D.W.; Tian, Y.K. Pharmacological inhibition of the NLRP3 in fl ammasome as a potential target for cancer-induced bone pain. *Pharmacol. Res.,* **2019**, *147*, 104339.
http://dx.doi.org/10.1016/j.phrs.2019.104339 PMID: 31276771

[43] Borghi, S.M.; Mizokami, S.S.; Pinho-Ribeiro, F.A.; Fattori, V.; Crespigio, J.; Clemente-Napimoga, J.T.; Napimoga, M.H.; Pitol, D.L.; Issa, J.P.M.; Fukada, S.Y.; Casagrande, R.; Verri, W.A., Jr The flavonoid quercetin inhibits titanium dioxide (TiO_2)-induced chronic arthritis in mice. *J. Nutr. Biochem.,* **2018**, *53*, 81-95.
http://dx.doi.org/10.1016/j.jnutbio.2017.10.010 PMID: 29197723

[44] Han, X.; Xu, T.; Fang, Q.; Zhang, H.; Yue, L.; Hu, G.; Sun, L. Quercetin hinders microglial activation to alleviate neurotoxicity *via* the interplay between NLRP3 inflammasome and mitophagy. *Redox Biol.,* **2021**, *44*, 102010.
http://dx.doi.org/10.1016/j.redox.2021.102010 PMID: 34082381

[45] Xu, D.; Hu, M.J.; Wang, Y.Q.; Cui, Y.L. Antioxidant activities of quercetin and its complexes for medicinal application. *Molecules,* **2019**, *24*(6), 1123.
http://dx.doi.org/10.3390/molecules24061123 PMID: 30901869

[46] Raygude, K.S.; Kandhare, A.D.; Ghosh, P.; Ghule, A.E.; Bodhankar, S.L. Evaluation of ameliorative effect of quercetin in experimental model of alcoholic neuropathy in rats. *Inflammopharmacology,* **2012**, *20*(6), 331-341.
http://dx.doi.org/10.1007/s10787-012-0122-z PMID: 22349996

[47] Calabrese, V.; Mancuso, C.; Calvani, M.; Rizzarelli, E.; Butterfield, D.A.; Giuffrida Stella, A.M. Nitric oxide in the central nervous system: Neuroprotection *versus* neurotoxicity. *Nat. Rev. Neurosci.,* **2007**, *8*(10), 766-775.
http://dx.doi.org/10.1038/nrn2214 PMID: 17882254

[48] Calabrese, V.; Cornelius, C.; Dinkova-Kostova, A.T.; Calabrese, E.J.; Mattson, M.P. Cellular stress responses, the hormesis paradigm, and vitagenes: Novel targets for therapeutic intervention in

neurodegenerative disorders. *Antioxid. Redox Signal.,* **2010**, *13*(11), 1763-1811.
http://dx.doi.org/10.1089/ars.2009.3074 PMID: 20446769

[49] Trovato Salinaro, A.; Pennisi, M.; Di Paola, R.; Scuto, M.; Crupi, R.; Cambria, M.T.; Ontario, M.L.; Tomasello, M.; Uva, M.; Maiolino, L.; Calabrese, E.J.; Cuzzocrea, S.; Calabrese, V. Neuroinflammation and neurohormesis in the pathogenesis of Alzheimer's disease and Alzheimer-linked pathologies: Modulation by nutritional mushrooms. *Immunity & ageing,* **2018**, 8.

[50] Mancuso, C.; Pani, G.; Calabrese, V. Bilirubin: An endogenous scavenger of nitric oxide and reactive nitrogen species, Redox report : Communications in free radical research. **2006**, *11*(5), 207-213.

[51] Miquel, S.; Champ, C.; Day, J.; Aarts, E.; Bahr, B.A.; Bakker, M.; Bánáti, D.; Calabrese, V.; Cederholm, T.; Cryan, J.; Dye, L.; Farrimond, J.A.; Korosi, A.; Layé, S.; Maudsley, S.; Milenkovic, D.; Mohajeri, M.H.; Sijben, J.; Solomon, A.; Spencer, J.P.E.; Thuret, S.; Vanden Berghe, W.; Vauzour, D.; Vellas, B.; Wesnes, K.; Willatts, P.; Wittenberg, R.; Geurts, L. Poor cognitive ageing: Vulnerabilities, mechanisms and the impact of nutritional interventions. *Ageing Res. Rev.,* **2018**, *42*, 40-55.
http://dx.doi.org/10.1016/j.arr.2017.12.004 PMID: 29248758

[52] Azevedo, M.I.; Pereira, A.F.; Nogueira, R.B.; Rolim, F.E.; Brito, G.A.C.; Wong, D.V.T.; Lima-Júnior, R.C.P.; de Albuquerque Ribeiro, R.; Vale, M.L. The antioxidant effects of the flavonoids rutin and quercetin inhibit oxaliplatin-induced chronic painful peripheral neuropathy. *Mol. Pain,* **2013**, *9*, 1744-8069-9-53.
http://dx.doi.org/10.1186/1744-8069-9-53 PMID: 24152430

[53] Sun, J.; Li, J.Y.; Zhang, L.Q.; Li, D.Y.; Wu, J.Y.; Gao, S.J.; Liu, D.Q.; Zhou, Y.Q.; Mei, W. Nrf2 activation attenuates chronic constriction injury-induced neuropathic pain *via* induction of PGC-1α-mediated mitochondrial biogenesis in the spinal cord. *Oxid. Med. Cell. Longev.,* **2021**, *2021*, 1-17.
http://dx.doi.org/10.1155/2021/9577874 PMID: 34721761

[54] Zhou, Y.; Liu, D.; Chen, S.; Chen, N.; Sun, J.; Wang, X.; Cao, F.; Tian, Y.; Ye, D. Nrf2 activation ameliorates mechanical allodynia in paclitaxel-induced neuropathic pain. *Acta Pharmacol. Sin.,* **2020**, *41*(8), 1041-1048.
http://dx.doi.org/10.1038/s41401-020-0394-6 PMID: 32203087

[55] Zhou, Y.Q.; Mei, W.; Tian, X.B.; Tian, Y.K.; Liu, D.Q.; Ye, D.W. The therapeutic potential of Nrf2 inducers in chronic pain: Evidence from preclinical studies. *Pharmacol. Ther.,* **2021**, *225*, 107846.
http://dx.doi.org/10.1016/j.pharmthera.2021.107846 PMID: 33819559

[56] Zhou, Y.Q.; Liu, D.Q.; Chen, S.P.; Chen, N.; Sun, J.; Wang, X.M.; Li, D.Y.; Tian, Y.K.; Ye, D.W. PPARgamma activation mitigates mechanical allodynia in paclitaxel-induced neuropathic pain *via* induction of Nrf2/HO-1 signaling pathway. **2020**, *129*, 110356.

[57] Bliss, T.V.P.; Collingridge, G.L.; Kaang, B.K.; Zhuo, M. Synaptic plasticity in the anterior cingulate cortex in acute and chronic pain. *Nat. Rev. Neurosci.,* **2016**, *17*(8), 485-496.
http://dx.doi.org/10.1038/nrn.2016.68 PMID: 27307118

[58] Luo, C.; Kuner, T.; Kuner, R. Synaptic plasticity in pathological pain. *Trends Neurosci.,* **2014**, *37*(6), 343-355.
http://dx.doi.org/10.1016/j.tins.2014.04.002 PMID: 24833289

[59] Wang, R.; Qiu, Z.; Wang, G.; Hu, Q.; Shi, N.; Zhang, Z.; Wu, Y.; Zhou, C. Quercetin attenuates diabetic neuropathic pain by inhibiting mTOR/p70S6K pathway-mediated changes of synaptic morphology and synaptic protein levels in spinal dorsal horn of db/db mice. *Eur. J. Pharmacol.,* **2020**, *882*, 173266.
http://dx.doi.org/10.1016/j.ejphar.2020.173266 PMID: 32553736

[60] Zeilhofer, H.U. Loss of glycinergic and GABAergic inhibition in chronic pain—contributions of inflammation and microglia. *Int. Immunopharmacol.,* **2008**, *8*(2), 182-187.
http://dx.doi.org/10.1016/j.intimp.2007.07.009 PMID: 18182224

[61] Fu, Q.; Shi, D.; Zhou, Y.; Zheng, H.; Xiang, H.; Tian, X.; Gao, F.; Manyande, A.; Cao, F.; Tian, Y.; Ye, D. MHC-I promotes apoptosis of GABAergic interneurons in the spinal dorsal horn and contributes to cancer induced bone pain. *Exp. Neurol.,* **2016**, *286*, 12-20.
http://dx.doi.org/10.1016/j.expneurol.2016.09.002 PMID: 27619625

[62] Zhou, Y.Q.; Chen, S.P.; Liu, D.Q.; Manyande, A.; Zhang, W.; Yang, S.B.; Xiong, B.R.; Fu, Q.C.; Song, Z.; Rittner, H.; Ye, D.W.; Tian, Y.K. The role of spinal GABAB receptors in cancer-induced bone pain in rats. *J. Pain,* **2017**, *18*(8), 933-946.
http://dx.doi.org/10.1016/j.jpain.2017.02.438 PMID: 28323246

[63] Filho, A.W.; Filho, V.C.; Olinger, L.; de Souza, M.M. Quercetin: Further investigation of its antinociceptive properties and mechanisms of action. *Arch. Pharm. Res.,* **2008**, *31*(6), 713-721.
http://dx.doi.org/10.1007/s12272-001-1217-2 PMID: 18563352

[64] Hossain, R.; Al-Khafaji, K.; Khan, R.A.; Sarkar, C.; Islam, M.S.; Dey, D.; Jain, D.; Faria, F.; Akbor, R.; Atolani, O.; Oliveira, S.M.R.; Siyadatpanah, A.; Pereira, M.L.; Islam, M.T. Quercetin and/or ascorbic acid modulatory effect on phenobarbital-induced sleeping mice possibly through $GABA_A$ and $GABA_B$ receptor interaction pathway. *Pharmaceuticals (Basel),* **2021**, *14*(8), 721.
http://dx.doi.org/10.3390/ph14080721 PMID: 34451819

[65] Bruehl, S.; Chung, O.Y. Parental history of chronic pain may be associated with impairments in endogenous opioid analgesic systems. *Pain,* **2006**, *124*(3), 287-294.
http://dx.doi.org/10.1016/j.pain.2006.04.018 PMID: 16725261

[66] Malafoglia, V.; Ilari, S.; Vitiello, L.; Tenti, M.; Balzani, E.; Muscoli, C.; Raffaeli, W.; Bonci, A. The interplay between chronic pain, opioids, and the immune system. *Neuroscientist,* **2021**, •••
http://dx.doi.org/10.1177/10738584211030493 PMID: 34269117

[67] Anjaneyulu, M.; Chopra, K. Quercetin, a bioflavonoid, attenuates thermal hyperalgesia in a mouse model of diabetic neuropathic pain. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2003**, *27*(6), 1001-1005.
http://dx.doi.org/10.1016/S0278-5846(03)00160-X PMID: 14499317

[68] Shimazu, R.; Anada, M.; Miyaguchi, A.; Nomi, Y.; Matsumoto, H. Evaluation of blood–brain barrier permeability of polyphenols, anthocyanins, and their metabolites. *J. Agric. Food Chem.,* **2021**, *69*(39), 11676-11686.
http://dx.doi.org/10.1021/acs.jafc.1c02898 PMID: 34555897

[69] Sivanesan, E.; Maher, D.P.; Raja, S.N.; Linderoth, B.; Guan, Y. Supraspinal mechanisms of spinal cord stimulation for modulation of pain. *Anesthesiology,* **2019**, *130*(4), 651-665.
http://dx.doi.org/10.1097/ALN.0000000000002353 PMID: 30556812

[70] Bannister, K.; Dickenson, A.H. Central nervous system targets: Supraspinal mechanisms of analgesia. *Neurotherapeutics,* **2020**, *17*(3), 839-845.
http://dx.doi.org/10.1007/s13311-020-00887-6 PMID: 32700132

[71] Mogil, J.S. Qualitative sex differences in pain processing: emerging evidence of a biased literature. *Nat. Rev. Neurosci.,* **2020**, *21*(7), 353-365.
http://dx.doi.org/10.1038/s41583-020-0310-6 PMID: 32440016

[72] Halievski, K.; Ghazisaeidi, S.; Salter, M.W. Sex-dependent mechanisms of chronic pain: A focus on microglia and P2X4R. *J. Pharmacol. Exp. Ther.,* **2020**, *375*(1), 202-209.
http://dx.doi.org/10.1124/jpet.120.265017 PMID: 32114512

[73] He, J.T.; Li, X.Y.; Zhao, X.; Liu, X. Hyperpolarization-activated and cyclic nucleotide-gated channel proteins as emerging new targets in neuropathic pain. *Rev. Neurosci.,* **2019**, *30*(6), 639-649.
http://dx.doi.org/10.1515/revneuro-2018-0094 PMID: 30768426

[74] Liu, F.; Wuni, G.Y.; Bahuva, R.; Shafiq, M.A.; Gattas, B.S.; Ibetoh, C.N.; Stratulat, E.; Gordon, D.K. Pacemaking activity in the peripheral nervous system: Physiology and roles of hyperpolarization activated and cyclic nucleotide-gated channels in neuropathic pain. *Cureus,* **2020**, *12*(10), e11111.
http://dx.doi.org/10.7759/cureus.11111 PMID: 33240707

[75] Liang, Y.; Xu, Z.; Wu, X.; Pang, J.; Zhou, P.; Cao, Y. Inhibition of hyperpolarization-activated cyclic nucleotide-gated channels with natural flavonoid quercetin. *Biochem. Biophys. Res. Commun.,* **2020**, *533*(4), 952-957.
http://dx.doi.org/10.1016/j.bbrc.2020.09.102 PMID: 33008592