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Potential Therapeutic Benefits of Curcumin in Treatment of Neuropathic Pain: An Indian Gold

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Abstract

CRM, an Indian gold is highly pleiotropic molecule as it exhibits many therapeutic benefits. It is interaction with numerous molecular targets enable them to considered it as potential drug molecules. Pre-clinical, Clinical and cell line studies have proven its use in diabetes, liver diseases, rheumatoid arthritis, neuropathic pain, various types of cancer and infectious diseases. The aforesaid activities of CRM are attributed to its direct interaction with DNA polymerase, focal adhesion kinase (FAK), protein kinase (PK) C, lipoxygenase (LOX), and tubulin etc. It has been reported also for the treatment of somatosensory defects leading to neuropathic pain. Despite its enormous potential, its therapeutic effects are underutilized. This may be attributed to its poor oral bioavailability due to its poor aqueous solubility and instability at intestinal pH. In the present review, clinical potential of CRM, its molecular targets, and various approaches to improve its efficacy and bioavailability for clinical applications have been discussed.

Keywords: CRM; molecular targets; neuropathic pain; bioavailability

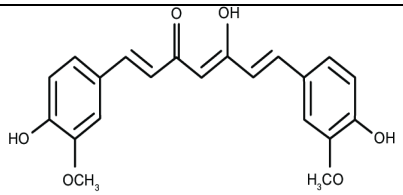
INTRODUCTION:

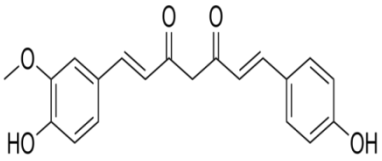
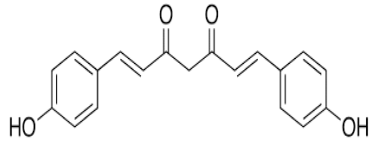
Curcumin (CRM) (*Curcuma Longa*) which belongs to the family *Zingibareacea* is a polyphenolic compound. There are total 133 species of the *Curcuma* worldwide.*[1]*. Some of the Species are:

- *Curcuma aeruginosa* (pink and blue ginger)
- *Curcuma amada* (mango ginger)
- Curcuma angustifolia (tall hidden ginger)
- *Curcuma aurantiaca* (rainbow curcuma)
- *Curcuma australasica* (Cape York turmeric)
- *Curcuma bicolo*r (candy corn)
- *Curcuma burttii*
- *Curcuma caesia*
- *Curcuma domestica* (Emperor variegated
- *Curcuma inodora* (pink ginger)
- *Curcuma kwangsiensis*
- *Curcuma lillicina* (pink cloud)
- *Curcuma zedoaria* (zedoary white turmeric)
- *Curcuma zanthorrhiza* (temulawak)
- *Curcuma yunnanensis* (Yunnan plume ginger)
- *Curcuma sumatrana* (Sumatra ginger)
- *Curcuma oligantha* (white turmeric)*[1]*

CRM is extract from the rhizome of the turmeric plant and it is the native of tropical South Asia. It is also known as 'Indian Saffron' because of its yellow color.[2]It is the natural flavonoid and the dietary substance of turmeric having wide range of therapeutic properties. Now a days CRM is also called as the golden spice because of having high potential in the modern medicine system for the treatment of number of diseases with high efficacy and less side effects and less toxic effect. CRM, demethoxy CRM and bisdemethoxy CRM are the main chemical constituents of the turmeric (Table.1.). These chemical constituents are collectively called as CRMoids which are polyphenolic compounds and are 3-6% present in turmeric.*[3]*

Table.1. Structures of chemical components of CRM

Sl. No.	**Chemical Constituents**	**Structure**	**Uses to treat**	**References**
1	CRM (80%)		Inflammation, cancer, spasm, emesis, ischemia, apoptotic, leukemia, inhibit leukotriene, Anti-nitrososaminic	[4-6]

2	Demethoxy CRM (15%)		Oxidation, infection due to bacteria and virus, inflammation, cancer	
3	Bisdemethoxy CRM (5%)			

CRM (diferuloylmethane) have various therapeutic properties such as dentistry, treatment for Inflammation, cancer, spasm, emesis, ischemia, apoptotic, leukemia, inhibit leukotriene, Anti-nitrososaminic, Oxidation, infection due to bacteria and virus, inflammation, cancer, astringents, anti-nociceptive and immunomodulation activity[6, 7]. A medicinal herb used by Indian in ancient time as a colorant and spice. Also deliver glimmering and gleam effect to skin in addition to dynamic and vitality to whole body. [6] According to the International Association for the Study of Pain (IASP) pain is basically an undesirable feeling which occurs due to damage of nerve [8] and a clinical state in which person shows symptoms of allodynia, hyperalgesia and akathisia like state is called as neuropathic pain (NP) [7]. People are gone through an emotional experience during pain. Today many peoples are suffering from pain with different experience which variesfrom person to person. Pain is the first indication to start taking the preventive steps to treat the disease. It is categorized as two type's acute and chronic pain but it is also categorize on the basis of damage like nociceptive pain due to damage of the tissue and NP is due to damage of the nerve. NP is defined as the pain which is defect of the somatosensory nervous system (peripheral and central nervous system) updated by the International Association for the Study of Pain (IASP). Perception of touch, vibration, pain, temperature, pressure and movement is associated with somatosensory nervous system. These nerves are crop up in the skin, muscles and joints. 7-10% of the total population is suffering from the NP and it can ascend from the different conditions like diabetic neuropathic pain (26%), HIVinfection, chemotherapy, leprosy, nerve injury and stroke. It affects the major parts of the human body that is brain and the spinal cord.[9] This pain can direct variation or jumbled the sensory transmission signals to the brain and the spinal cord. It also has influence on the quality of the patient's life as well as social and economic aspects. CRM shows its effect by directly interacting with EGFR, CXCR4 related receptors. Several other components like growth factors (e.g., EGF, TGFβ), kinases (e.g., MAPK, FAK), transcription factors (e.g., NF-κβ, STAT1-5), enzymes (e.g., DNA pol, COX2), adhesion molecules (e.g., ICAM-1, VCAM-1), apoptotic regulators (e.g., survivin, Bcl-2), pro inflammatory cytokines (e.g., interleukin (IL)-8, tumor necrosis factor (TNF) [10, 11] are also responsible for CRM activity.

Therapeutic benefits of CRM

Neutraceuticals: means "Nutrition" and "Pharmaceutical" invented by *Stephen De Felice* products are alterative to pharmaceutical having physiological aids. Neutraceuticals is a "food" said by *Felice*which is a new era of the medicine system which includes the natural product

focusing on the preventions and protection of diseasesmostly for the elder persons and for growth and development of the children also for women and youngsters who are fitness freak these are natural products, dietary supplements and functional food.[12]It is a novel medicine system. Neutraceuticals Natural food bases of the neutraceuticals are:

- Dietary Supplements
- Probiotic
- Prebiotics
- Polyphenols
- Antioxidants
- Fatty acids(Poly-unsaturated)

Broadly they are classified as:

- Potential Neutraceuticals
- Established Neutraceuticals[12]

The main focus of the neutraceuticals in the pharmaceutical is to increase the absorption and bioavailability of the drug to give its effective response and to make drug more efficient. It shows low side effects and having non-toxics compounds which provides potential nutrition, therapeutic and physiological effects. Nutraceuticals substance developing from contribution of food, herbo-dietry, pharmaceutical and agriculture based industries [13]. CRM (1,7-bis (hydroxyl-3-methoxyphenyl) -1,6-heptadiene-3,5-dione), is a vital active polyphenolic constituent and turmeric therapeutic benefits depends on it.[14]. CRM have number of pharmacological activities for different kinds of diseases and health condition (Figure.1.). Pharmacological studies involve the pharmacodynamics and pharmacokinetic study of the drug. This includes the evaluation of the safety, efficacy, toxicity and cellular level mechanism of the drug. To evaluate all these drugs are studied on different models shown in table2.

Figure.1. Multiple uses of CRM [15-19]

Table.2. Pharmacological responses of CRM

Sl. No.	Activity	Mechanism	Reference
1	Anti-inflammatory	inhibit cytokine, tumor necrosis factor-alpha (TNF-α), COX-2, histamine, prostaglandins, leukotriene, oxygen- and nitrogen-derived free radicals	[20], [21]
2	Anti-oxidant	Inhibiting lipid degradation, lipid peroxidation and cytolysis, inhibits low-density lipoprotein, showed prominent effect in 1,1-diphenyl-2-picryl hydrazyl free radical (DPPH), 2,2′-azino-bis(3-ethylbenzthiazoline-6sulfonic acid) (ABTS), N, N-dimethyl-p-phenylenediamine di-hydrochloride (DMPD) radical scavenging activity	[22], [23], [16], [24]
3	Wound Healing	Wound healing by enhancing cell proliferation, fibroblast, fibronectin expression, synthesis and deposition of collagen.	[22]
4	Anti-diabetic	Due to anti-oxidant activity, by dropping the building of the super oxides and inhibits the protein kinase, suppresses the serum level of TNF-Alpha and interleukins regenerates pancreatic activity	[16], [17]
5	Anti-cancer	CRM exert potent anti- proliferative properties against various types of tumor. In in-vitro studies CRM shows its effect by suppression of nuclear factor-nB (NF-nB) and inhibit angiogenesis process.	[25]
6	Anti-Angiogenesis	CRM also have anti-angiogenesis property by inhibiting basic fibroblast growth factor (bFGF)	[17]

Preclinical Studies of CRM for neuropathic pain:

Good laboratory practices are the guideline to perform the preclinical trials. Basically it is use to study the pharmacokinetic parameters of the drug on animal model before studying it on humans. Preclinical studies can help to evaluate the safety, efficacy, toxicity, dosing and biological effects of the drug in in-vivo and in-vitro study. This information is furthermore use when to perform the clinical trials [26]. Some of the preclinical studies related to CRM are shown below in the table 3:

Table.3. Preclinical Studies of CRM for neuropathic pain

S. No:	Animal	Model	Formulation	Doses	Mechanism	Reference
1	Adult male sprague dawley.	Chronic Constriction Injury model	CRM suspension in 0.5% of carboxymet	1ml/100 g of body weight	Behavioral allodynia mechanical test is done. CRM reversed the mechanical allodynia.	[27]

	(weight of 280-320g)		hylcellulose.			
2	Male sprague dawley(wright 250-270g)	STZ induced Diabetic Neuropathic model	Self Nano Emulsify Drug Delivery System	30,100 and 300mg/Kg	• Inhibit release of tissue necrosis factor-alpha • Inhibit release of nitric oxide • Reduce allodynia and hyperglasia.	[28]
3	Adult male Sprague–Dawley rats (weighing from 200-240g)	Nerve injury in diabetic rat model	-	50, 100 and 300mg/kg	• Increased the number of FG-labeled motoneurons in diabetic rats. • Increased the premotor functions and sensational functions.	[29]
4	Male sprague dawley (wright 160-180g)	Type-2 diabetes mellitus model	-	100mg/kg	CRM reduced the amplitude of TTX-R Ina(tetrodotoxin)	[30]
5	Adult male mice	Chronic Constriction Injury model	-	Chronic CRM treatment 5, 15 and 45mg/kg intraperitoneal route.	• Anti-allodynic action by chronic CRM with beta-2 adrenoceptor antagonist. • Anti-hyperglasic action on thermal stimuli.	[7]
6	Male Sprague-Dawley rats (250–300 g)	postoperative pain model	Suspended in 0.5% carboxymethylcellulose	2ml/kg	• CRM could promote recovery from the surgery. • Anti-hyperalgesic effects.	[31]
7	Wistar rats of either sex (180–270	Alcoholic induced neuropathic model	CRM + Ethanol	30 and 60mg/kg	• Increased serotonin, norepinephrine, dopamine levels • Adenosine	[32]

	g)				triphosphate-sensitive potassium (KATP) channels activation	
8	Adult male Wistar rats (Weight of 150–200 g)	Alcoholic induced neuropathic model	CRM + Ethanol	20,40 and 80mg/kg	• CRM inhibit pro-inflammatory mediators like TNF- and IL-1. • Enhanced paw withdraw threshold. • Enhanced tail withdraws latency.	[33]
9	Sprague-Dawley rats	Brachial plexus avulsion model.	CRM + 20% dimethyl sulfoxide (DMSO)	60mg/kg	• Reduced cold allodynia effect. • Down regulates the effect of proinflammatory cytokines(IL-1β, IL-6, and TNF-α) • Inhibition of c-Fos and nerve growth factor.	[34]
10	Female Swiss Webster mice	Diabetic neuropathic model	-	50mg/kg	• Enhanced allodynic effect • Increased the hind paw withdrawal latency induced by ethanol	[35]
11	Male albino mice of Laka strain (20–30 g)	Diabetic neuropathic mice model	CRM + 0.5% car boxy methylcellulose solution i.e. suspension	15, 30, and 60mg/kg	• Reduction of TNF-α and release of nitric oxide	[36]
12	60 male Sprague-Dawley rats (220–250 g)	Chronic Constriction Injury model	CRM dissolved in 20% dimethyl sulfoxide (DMSO) with 80% normal saline	20, 40 or 60 mg/kg	• Down-regulating the p300/CBP (cAMP response binding protein) • HAT (Histone acetyltransferase) influenced gene expression of Brain derived neuropathic	[37]

			solution		factor (BDNF) and Cox-2.	
13	Male Sprague-Dawley rats with initial weights of 250–300 g	chronic constriction injury model	CRM was suspended in 0.5% carboxymethylcellulose	10-40mg/kg	• Anti-hyperalgesic effect	[31]
14	Adult male Sprague-Dawley rats of weight 200–220 g	Streptozocin induced diabetic neuropathic model	-	200 mg/kg	• CRM suppress the NADPH oxidative which produced reactive oxygen species.	[38]
15	Male Sprague-Dawley rats weighing 180–220 g	Streptozocin induced type-2 diabetic neuropathic model	Nanoparticle-encapsulated CRM	16 mg/kg	• CRM decreased the up-regulation of P2Y12 expression levels • Reduced the up-regulation of IL-1β and Cx43	[39]
16	Male albino mice of Laka strain (20–30 g)	Streptozocin induced diabetic neuropathic model	CRM and resveratrol suspensions were prepared in 0.5% carboxy-methylcellulose solution.	60 mg/kg	• Reduced the serum TNF-α level which is markedly increased in diabetes. • Reduced allodynia and hyperalgesia effect in diabetic neuropathic model.	[40]
17	30 adult male Wistar rats (200–220 g)	Vincristine induced neuropathic model	-	40 and 80 mg/kg	• Decreased latency period of paw removal • Reduced Hyperalgesia effect which was enhanced by vincristine • Improved sciatic functional index and motor nerve conduction velocity.	[41]

18	Sprague-Dawley rats (250 and 300 g)	Capsaicin-induced Thermal Hyperalgesia	CRM + 70% DMSO	(5, 25, or 50 mg/mL/kg	• Capsaicin-induced current in trigeminal ganglion neurons blocked by CRM • Transient receptor potential vanilloid 1 (TRPV1) mediated currents in Human embryonic kidney (HEK) blocked by CRM	[42]
19	Male mice weighing 30–35 g.	chronic constriction injury model	-	10mg/kg	• Transient receptor potential vanilloid type 1 blocked by KMS4034 a CRMoid	[43]
20	30 Adult male rat of weight 180 – 220g	Streptozocin incudes diabetic neuropathic pain model	-	10 μM and 100 μM	• Enhanced mechanical withdraw threshold	[44]
21	Adult male Sprague–Dawley rats (280–300g)	Streptozocin incudes diabetic neuropathic pain model	-	100mg/kg	• CRM increase the hyperalgesia effect which was enhanced by the Streptozocin.	[45]
22	Male albino rat (8-9 weeks old)	Acrylamide induced neuropathic pain	-	50mg/kg	• Elevate the level of biosynthesis of glutathione • Enhanced hyperalgesia activity • Elevated the level of oxidative markers like hyper oxides and reactive oxygen species	[46]

Clinical Studies of CRM for neuropathic pain:

Clinical studies are used to evaluate the pharmacodynamics and pharmacokinetic parameters of the drug on the human model. Centre for Clinical Trials and Data Coordination (CCDC) is one of origination for the smooth conduct of the clinical trials was establishes in 2015. CCDC focus on:

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- Design of the study
- Conduct and coordinate the study
- Analysis of the study
- Authorized person for study
- Data coordination center grant[47]

Clinical study of the CRM shown below:

Table.4.Clinical Studies of CRM for neuropathic pain

S. No:	Patients	Model	Formulation	Doses	Mechanism	Reference
1	80 patients Age: 30-60 years Body mass index: 25-39.9 kg/m^3	Non-insulin dependent diabetes mellitus	Placebo capsule consists of polysorbate 80	80mg	CRM inhibits the production of pro-inflammatory cytokines and synthesis of nitric oxide.	[48]
2	141 patients from these 135 completed the study	Neuropathic pain model	In the form of Phytosomes	400 mg	Shows anti-inflammatory activity by inhibiting cox-2.	[49]

Cell-line study of CRM on neuropathic pain:

For the study of disease screening, cytotoxicity, delivery system of the drug (mechanism of the drug) and permeability of the drug cell line studies (study using the cell culture) is an imperative podium. It can be done in 2-dimensional and 3-dimensional study. Cell line study also contributes in reduction of the cost and the use of animal is also reduced. Cell line study is the easy accessibility to study the cell level mechanism of the drug. There is cell line study of the CRM shown below in the table: [50, 51]

Table.5.Cell line study of CRM

S. No:	Cell-line tissue	Model	Dose	Mechanism	Reference
1	Adult Drosophila Melanogaster male of 8-10 days	Acrylamide induced neuropathic pain	5-10 μM	CRM significantly increase the level of glutathione and total thiol which was reduced by the acrylamide.	[52]

2	RSC96 cells (Dulbecco's Modified Eagle's Medium is used to culture the cells)	Streptozocin incudes diabetic peripheral neuropathic pain model	10 and 100 μM	• Adenosine 5'-monophosphate-activated protein kinase level was increases. • Transient receptor potential A1 regulation was reduced by CRM.	[44]

Conclusion:

Herbal treatment gives therapeutic benefits at a slow rate but they are safer with respect to synthetic drugs. CRM is a golden spice many of the research work going on continuously and they used to give good preclinical and clinical responses. Even patents filed using CRM indicates that how significantly it is important for health related issues.

Reference:

1. Prasad, S. and B.B. Aggarwal, *Turmeric, the golden spice: from traditional medicine to modern medicine.* 2011.
2. Chattopadhyay, I., et al., *Turmeric and curcumin: Biological actions and medicinal applications.* CURRENT SCIENCE-BANGALORE-, 2004. **87**: p. 44-53.
3. Niranjan, A. and D. Prakash, *Chemical constituents and biological activities of turmeric (Curcuma longa l.)-a review.* Journal of Food Science and Technology, 2008. **45**(2): p. 109.
4. Sandur, S.K., et al., *Curcumin, demethoxycurcumin, bisdemethoxycurcumin, tetrahydrocurcumin and turmerones differentially regulate anti-inflammatory and anti-proliferative responses through a ROS-independent mechanism.* Carcinogenesis, 2007. **28**(8): p. 1765-1773.
5. Ireson, C., et al., *Characterization of metabolites of the chemopreventive agent curcumin in human and rat hepatocytes and in the rat in vivo, and evaluation of their ability to inhibit phorbol ester-induced prostaglandin E2 production.* Cancer research, 2001. **61**(3): p. 1058-1064.
6. AloK, A., et al., *Curcumin–pharmacological actions and its role in oral submucous fibrosis: a review.* Journal of clinical and diagnostic research: JCDR, 2015. **9**(10): p. ZE01.
7. Zhao, X., et al., *Curcumin exerts antinociceptive effects in a mouse model of neuropathic pain: descending monoamine system and opioid receptors are differentially involved.* Neuropharmacology, 2012. **62**(2): p. 843-854.
8. Murnion, B.P., *Neuropathic pain: current definition and review of drug treatment.* Australian prescriber, 2018. **41**(3): p. 60.
9. Bates, D., et al., *A Comprehensive Algorithm for Management of Neuropathic Pain.* Pain Medicine, 2019. **20**(Supplement_1): p. S2-S12.
10. Bielak-Zmijewska, A., et al., *The role of curcumin in the modulation of ageing.* International journal of molecular sciences, 2019. **20**(5): p. 1239.

11. Kunnumakkara, A.B., et al., *Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases.* British journal of pharmacology, 2017. **174**(11): p. 1325-1348.
12. Das, L., et al., *Role of nutraceuticals in human health.* Journal of food science and technology, 2012. **49**(2): p. 173-183.
13. Malik, A., et al., *The potentials of Nutraceuticals.* Pharmainfo. net, 2008. **6**: p. 151-183.
14. Nagpal, M. and S. Sood, *Role of curcumin in systemic and oral health: An overview.* Journal of natural science, biology, and medicine, 2013. **4**(1): p. 3.
15. Aggarwal, B.B., A. Kumar, and A.C. Bharti, *Anticancer potential of curcumin: preclinical and clinical studies.* Anticancer research, 2003. **23**(1/A): p. 363-398.
16. Alsamydai, A. and N. Jaber, *Pharmacological aspects of curcumin: Review article.* Int. J. Pharmacogn, 2018. **5**: p. 313-326.
17. Beevers, C.S. and S. Huang, *Pharmacological and clinical properties of curcumin.* Botanics: Targets and Therapy, 2011. **1**(5).
18. Aggarwal, B.B. and B. Sung, *Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets.* Trends in pharmacological sciences, 2009. **30**(2): p. 85-94.
19. Araujo, C. and L. Leon, *Biological activities of Curcuma longa L.* Memórias do Instituto Oswaldo Cruz, 2001. **96**(5): p. 723-728.
20. Abdulkhaleq, L., et al., *The crucial roles of inflammatory mediators in inflammation: A review.* Veterinary world, 2018. **11**(5): p. 627.
21. Jacob, A., et al., *Mechanism of the anti-inflammatory effect of curcumin: PPAR-γ activation.* PPAR research, 2007. **2007**.
22. Maheshwari, R.K., et al., *Multiple biological activities of curcumin: a short review.* Life sciences, 2006. **78**(18): p. 2081-2087.
23. Shen, L. and H.-F. Ji, *The pharmacology of curcumin: is it the degradation products?* Trends in molecular medicine, 2012. **18**(3): p. 138-144.
24. David, B., J.-L. Wolfender, and D.A. Dias, *The pharmaceutical industry and natural products: historical status and new trends.* Phytochemistry Reviews, 2015. **14**(2): p. 299-315.
25. Mullaicharam, A. and A. Maheswaran, *Pharmacological effects of curcumin.* International Journal of Nutrition, Pharmacology, Neurological Diseases, 2012. **2**(2): p. 92.
26. Honek, J., *Preclinical research in drug development.* Medical Writing, 2017. **26**: p. 5-8.
27. Jeon, Y., et al., *Curcumin could prevent the development of chronic neuropathic pain in rats with peripheral nerve injury.* Current Therapeutic Research, 2013. **74**: p. 1-4.
28. Joshi, R.P., et al., *SNEDDS curcumin formulation leads to enhanced protection from pain and functional deficits associated with diabetic neuropathy: an insight into its mechanism for neuroprotection.* Nanomedicine: Nanotechnology, Biology and Medicine, 2013. **9**(6): p. 776-785.
29. Ma, J., et al., *Curcumin promotes nerve regeneration and functional recovery after sciatic nerve crush injury in diabetic rats.* Neuroscience letters, 2016. **610**: p. 139-143.
30. Meng, B., et al., *Effects of curcumin on TTX-R sodium currents of dorsal root ganglion neurons in type 2 diabetic rats with diabetic neuropathic pain.* Neuroscience letters, 2015. **605**: p. 59-64.

31. Zhu, Q., et al., *Antinociceptive effects of curcumin in a rat model of postoperative pain.* Scientific reports, 2014. **4**: p. 4932.
32. Kaur, M., et al., *Protective effect of co-administration of curcumin and sildenafil in alcohol induced neuropathy in rats.* European journal of pharmacology, 2017. **805**: p. 58-66.
33. Kandhare, A.D., et al., *Therapeutic role of curcumin in prevention of biochemical and behavioral aberration induced by alcoholic neuropathy in laboratory animals.* Neuroscience letters, 2012. **511**(1): p. 18-22.
34. Xie, W., et al., *Administration of Curcumin Alleviates Neuropathic Pain in a Rat Model of Brachial Plexus Avulsion.* Pharmacology, 2019. **103**(5-6): p. 324-332.
35. Daugherty, D.J., et al., *A novel curcumin derivative for the treatment of diabetic neuropathy.* Neuropharmacology, 2018. **129**: p. 26-35.
36. Sharma, S., et al., *Curcumin attenuates thermal hyperalgesia in a diabetic mouse model of neuropathic pain.* European journal of pharmacology, 2006. **536**(3): p. 256-261.
37. Zhu, X., et al., *Curcumin alleviates neuropathic pain by inhibiting p300/CBP histone acetyltransferase activity-regulated expression of BDNF and cox-2 in a rat model.* PloS one, 2014. **9**(3): p. e91303.
38. Zhao, W.-C., et al., *Curcumin ameliorated diabetic neuropathy partially by inhibition of NADPH oxidase mediating oxidative stress in the spinal cord.* Neuroscience letters, 2014. **560**: p. 81-85.
39. Jia, T., et al., *Nanoparticle-encapsulated curcumin inhibits diabetic neuropathic pain involving the P2Y12 receptor in the dorsal root ganglia.* Frontiers in neuroscience, 2018. **11**: p. 755.
40. Sharma, S., K. Chopra, and S.K. Kulkarni, *Effect of insulin and its combination with resveratrol or curcumin in attenuation of diabetic neuropathic pain: participation of nitric oxide and TNF-alpha.* Phytotherapy Research, 2007. **21**(3): p. 278-283.
41. Greeshma, N., K. Prasanth, and B. Balaji, *Tetrahydrocurcumin exerts protective effect on vincristine induced neuropathy: behavioral, biochemical, neurophysiological and histological evidence.* Chemico-biological interactions, 2015. **238**: p. 118-128.
42. Yeon, K., et al., *Curcumin produces an antihyperalgesic effect via antagonism of TRPV1.* Journal of dental research, 2010. **89**(2): p. 170-174.
43. Lee, J., et al., *Antinociceptive curcuminoid, KMS4034, effects on inflammatory and neuropathic pain likely via modulating TRPV1 in mice.* British journal of anaesthesia, 2013. **111**(4): p. 667-672.
44. Lv, J., et al., *A curcumin derivative J147 ameliorates diabetic peripheral neuropathy in streptozotocin (STZ)-induced DPN rat models through negative regulation AMPK on TRPA1.* Acta cirurgica brasileira, 2018. **33**(6): p. 533-541.
45. Attia, H.N., et al., *Protective effects of combined therapy of gliclazide with curcumin in experimental diabetic neuropathy in rats.* Behavioural pharmacology, 2012. **23**(2): p. 153-161.
46. Prasad, S.N., *Mitigation of acrylamide-induced behavioral deficits, oxidative impairments and neurotoxicity by oral supplements of geraniol (a monoterpene) in a rat model.* Chemico-biological interactions, 2014. **223**: p. 27-37.

47. Abebe, K.Z., et al., *Creating an academic research organization to efficiently design, conduct, coordinate, and analyze clinical trials: The Center for Clinical Trials & Data Coordination.* Contemporary Clinical Trials Communications, 2019: p. 100488.
48. Asadi, S., et al., *Nano curcumin supplementation reduced the severity of diabetic sensorimotor polyneuropathy in patients with type 2 diabetes mellitus: A randomized double-blind placebo-controlled clinical trial.* Complementary therapies in medicine, 2019. **43**: p. 253-260.
49. Di Pierro, F. and R. Settembre, *Safety and efficacy of an add-on therapy with curcumin phytosome and piperine and/or lipoic acid in subjects with a diagnosis of peripheral neuropathy treated with dexibuprofen.* Journal of pain research, 2013. **6**: p. 497.
50. Allen, D.D., et al., *Cell lines as in vitro models for drug screening and toxicity studies.* Drug development and industrial pharmacy, 2005. **31**(8): p. 757-768.
51. ŞAHİN, Ş.H.T., B. MESUT, and Y. ÖZSOY, *Applications of Cell Culture Studies in Pharmaceutical Technology.* ACTA Pharmaceutica Sciencia. **55**(3).
52. Prasad, S.N., *Neuroprotective effect of geraniol and curcumin in an acrylamide model of neurotoxicity in Drosophila melanogaster: relevance to neuropathy.* Journal of insect physiology, 2014. **60**: p. 7-16.

