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The Disadvantages Of Curcumin Based On Its Phytochemical Composition And Anti-Inflammatory Activity In Peripheral Nerve Regeneration In Sciatic Nerve Injury

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Abstract

BACKGROUND: Illnesses related to the somatosensory system, lesion, or even sciatic nerve injury result in the emergence of neuropathic-related pain, a fact that calls for the need of carrying out a peripheral nerve regeneration, especially in curing the resultant pain due to the sciatic nerve injury. This form of injury relates to peripheral neuropathic pain, and therefore, it comprises of the rapture of or the damage to the peripheral nervous system. It is worth acknowledging that approximately 10-15% of people experience an acute form of postoperative pain and subsequent constant pains after taking surgery procedures. Such instances often call for the application of anticonvulsants, clonidine, baclofen, and antidepressants as treatment remedies and approaches of thwarting and ending peripheral neuropathy, as opioids apply in the treatment of postoperative pain.

AIM: This study aimed to discuss the disadvantages of using Curcumin as treatment mitigation in peripheral nerve regeneration in sciatic nerve injury based on its anti-inflammatory activity and phytochemical composition.

METHODS: The study ~~that~~ used in this method was quantitative research.

RESULTS: The application of these drugs, however, presents some negative effects. As such, there is the necessity of soliciting better therapeutics as alternatives, especially those that have limited to no side effects and improved efficacy. This

consideration presents the need to implement the use of Curcumin. As a polyphenol generated from the Curcuma longa roots, Curcumin has anti-inflammatory, antioxidant, and antibacterial medical properties. Additionally, the adoption of Curcumin presents a faster rate of metabolism and reduced bioavailability; both of them have resulted in the establishment of different formulations of Curcumin. The need to implement Curcumin and its associated formulations as medical remedies to postoperative and neuropathic pains elevate the significance of comprehensive analysesof its effects regarding their reliability to perfect execution of such health functions. As per the positive results obtained from both clinical and preclinical pieces of research, Curcumin reflects a quite considerate degree of reliability as a mitigation or health remedy appropriate in the prevention of postoperative and neuropathic pain conditions. Therefore, the disadvantages associated with the use of Curcumin in the peripheral regeneration of nerve in sciatic nerve injuries avails the need to improve its formulations so that its health side effects as post-operative and neuropathic drugs can be lowered as far as possible for their reliable and effective medical application.

CONCLUSION: The case for peripheral nerve injury patients was not 100% reliable curcumin as a remedy, but it makessome assumptionsof some disadvantages during its administration unto the patients.It is necessary to establish a curcumin formulation with minimal to no post-surgery pains and aftermath of Curcumin-related health complications.

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Introduction

Sciatic nerve injury in individuals attracts the medical regeneration of nerve peripheries. This type of injury categorizes as a neuropathic form of pain. Neuropathic pain refers to a procedure or occurrence after a primary disease or lesion of the somatosensory nervous system.According to either voluntarily-made self-reports or clinical studies, neuropathic pain during peripheral nerve regeneration in sciatic nerve injuries prevails in the United States of America. This prevalence occurs at the rate of 12.4% and 9.8% for the voluntarily self-made reports and clinical research. Since there is a relative range of differences regarding the definition of sciatic nerve injury neuropathic pain, besides adopting various epidemiological assessment approaches, it is quite tough to present more accurate approximations of neuropathic pain.Peripheral neuropathic pain is the injuries on or the damage of the peripheral nerves. As per the reports relayed by various research bodies, such as the Special Interest Group (on Neuropathic Pain), selective serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, andgabapentinoidsare identified as primary drugs in the treatment of sciatic nerve injury neuropathic pain, like tramadol, capsaicin, and lidocaine as ~~being~~ the secondary ones.Also, botulinum toxin-A, oxycodone, and morphine are categorized as peripheral neuropathic pain's third-line medical interventions [1].Despite the existence of the above drugs as first-, second-, and third-line forms of the sciatic nerve injury neuropathic pain treatment medical remedies, they possess many side effects, which

constricts the range and frequencies of their applications as treatment options or prevention measures against the sciatic nerve injury neuropathic pain [2]. The rise of these concerns elevates the option of Curcumin and its formulations as the best available form of treatment against sciatic nerve injury neuropathic pain. The reason ~~being~~ is ~~that~~ Curcumin presents decreased magnitudes of side effects as a treatment remedy when compared to the known first-, second-, and third-line types of the sciatic nerve injury neuropathic pain treatment medical remedies. Additionally, curcumin formulations can also undergo some improvements as much as possible to reduce its side effects on patients' health. Despite the possibility of these adjustments, the adoption of Curcumin and its formulations as treatment in peripheral nerve regeneration in sciatic nerve injury still presents some disadvantages due to its anti-inflammatory activity and phytochemical composition. The paper, therefore, discusses the disadvantages of using Curcumin as a mitigation treatment in peripheral nerve regeneration in sciatic nerve injury based on its anti-inflammatory activity and phytochemical composition.

Methods

The study ~~that~~ used in this method was quantitative research. The results of the quantitative research study were shown in Table 1.

Table 1: Research Methods and Results

The Method of Research	The Research Results
Qualitative Research	• Curcumin has a low bioavailability [1] • Curcumin is practically insoluble in aqueous form and therefore relative [3] • Curcumin has a rapid metabolism [1] • Curcumin and its formulations reduce nerve sensibilities [3] • Curcumin boosts peripheral nerve regeneration [3] • Curcumin has chemotherapy-Induced Peripheral Neuropathy [1]

Results and Discussion

Research Methodology for Evaluating Treatment Properties of Curcumin against Sciatic Nerve Injury among Peripheral Neuropathies

The method of many research studies has been carried out in rats and humans to assert Curcumin's properties during its administration as a medical treatment remedy for peripheral nerve regeneration in sciatic nerve injury, among other peripheral neuropathic pains. These properties include Curcumin's bioavailability, stability and solubility, rapid metabolism, sensitivity loss traits, peripheral nerve regeneration uncertainties, chemotherapy-related peripheral neuropathy, alcoholic properties, ~~and~~ postoperative pains, and among other qualities.

As per the rats in which oral delivery of Curcumin had been administered, most of the Curcumin in ingestion excretes in the form of feces, accounting for the weak bioavailability that it demonstrates as a property [4].Just minimal magnitudes of Curcumin have their absorption with the parts of intestines and excretes in the urine medium [5]. Also, according to pharmacokinetics research carried out in rats, oral Curcumin's bioavailability is somewhere close to 1%. For example, the highest concentration (Chighest) in only in 500ng/mL of serum had to be reported after 1g/kg of Curcumin had been delivered orally. In another research study, the value of the highest concentration (Chighest) was 60ng/mL after 0.5g/kg of Curcumin had been administered orally. In contrast, the highest concentration of serum that had to be reached was 360ng/mL, after Curcumin of 10mg/kg had been delivered [1]. In human beings, the value of the highest concentration (Chighest) of 50ng/mL had been reported due to the escalated doses to 12g from 500mg of Curcumin after an oral administration [6].

Some research studies also had diabetes developed in rats through applying streptozotocin (50 mg/kg) in a single dose [1]. The diabetic rats were then administered with Curcumin in doses of 50, 100, and 300mg/kg daily (intraperitoneally) from a period of 4 weeks after the nerve crush injury or with normal saline [7]. The regeneration of axons had to be investigated by retrograde labeling and morphometric analysis. There was then an evaluation of recovery of function by analysis of behavior and electrophysiological studies. Curcumin significantly enhanced the recovery of functions and the regeneration of axons and was potentially better than the ones in saline group vehicles. Additionally, extreme curcumin doses (100 and 300mg/kg) achieved improved recovery of functions and regeneration of axons better than the 50mg/kg dose [1].

Findings on Curcumin Formulations, Origin, Chemical Composition and Structure

Curcumin and Its Formulations as A Treatment Remedy in The Peripheral NerveRegeneration in Sciatic Nerve Injury

The main clinical constraint in peripheral nerve regeneration in sciatic nerve injury during treatment procedures associated with peripheral neuropathies is the poor administration of treatment measures with the contemporarily existing therapeutics, besides the complexities experienced during the understanding and diagnosing the pathological approaches applied in the entire process. In effect, current research studies have managed to propose some potential treatment methods concerning preventing and curing several inflammatory illnesses, and these primarily include Curcumin and its related formulations. Curcumin as an attractive molecule has for a long time been applied traditionally as Asian medicine and cuisine [3]. However, it has a speedy rate of metabolism and an extremely low bioavailability [8]. These two properties make its medical administration only possible in high doses to attain the required therapeutic results and effects due to the uncertainties regarding whether and how fast it will finally reach the body organs in the target [9].

Curcumin, also regarded as diferuloylmethane, with a chemical representation of 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, occurs as a polyphenol that exists in Curcuma longa's rhizome. The powder form of Curcuma longa occurs as a spice called turmeric and applies in preparing curry. Turmeric powder occurs in a crystalline compound that is orange-yellow and is an agent of food coloring [3]. In traditional aspects, turmeric powder applied in Asian nations is a medically-initiated preparation against combating multiple illnesses due to its anti-inflammatory, neuroprotective, anticancer, antioxidant, and antimicrobial properties [4]. The Enol B and Keto A Forms of Curcumin were shown in Figure 1.

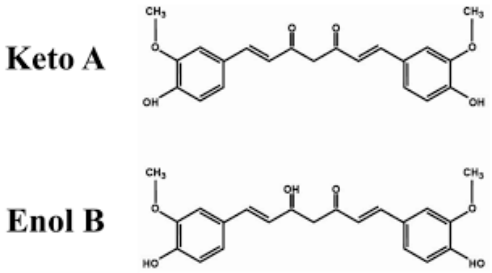

Figure 1: The Enol B and Keto A Forms of Curcumin [1].

For the past half-a-century, it has been evident that most of Curcuma longa's effects are mainly because of its curcumin composition, with significant crucial characteristics against arthritis, allergies, neuropathies, diabetes, among other chronic illnesses. However, other compositions of Curcuma longa are in existence, in combination with Curcumin, constitute the curcuminoid group, which are

bisdemethoxycurcumin and demethoxycurcumin. The curcuminoid group comprises nearly 5% of the entire Curcuma longa's components, and Curcumin stands to be the major component with 77% abundance in the group [3]. These compositional properties attribute to the preclinical and clinical applications of Curcumin as a treatment remedy against the peripheral nerve regeneration in sciatic nerve injury, among other existing peripheral neuropathies, and its benefits even in future therapeutic applications. The Mimics of Curcumin Monocarbonyl was shown in Figure 2.

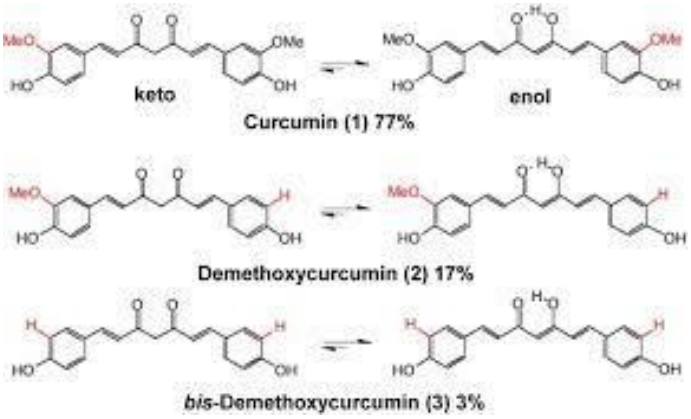

Figure 2: The Mimics of Curcumin Monocarbonyl [3].

Results and Discussion

Disadvantages of Using Curcumin and Its Formulations as A Treatment Remedy in The Peripheral Nerve Regeneration in Sciatic Nerve Injury

Bioavailability of Curcumin

Curcumin has a low bioavailability, which has received extensive proof reports, especially in humans and rodents. It is characterized as having a speedy metabolism rate, rapid excretion rate, and poor absorption in the body [10]. As per the studies carried out in rats (due to oral delivery of Curcumin), most of the Curcumin in ingestion excretes in the form of feces, accounting for the weak bioavailability that it demonstrates as a property [4]. Just minimal magnitudes of Curcumin have their absorption with the parts of intestines and excretes in the urine medium [5]. Also, according to pharmacokinetics research carried out in rats, oral Curcumin's bioavailability is somewhere close to 1% [1]. This, in conjunction with the raised degree of retro-enteral and intestinal retention efflux, has a translation of extremely minimal levels of Curcumin in the tissue [11]. Curcumin distribution throughout the body as research in rats reveals a strong tissue distribution variability [12].

Stability and Solubility

The therapeutic effectiveness of Curcumin as a remedy in the peripheral nerve regeneration in sciatic nerve injury and other associated peripheral neuropathies portrays some applicational restrictions since it has a reduced solubility while in an aqueous medium [3]. It also has unfavorable pharmacokinetics, specifically unfavorable distribution, absorption, excretion and metabolism, and chemically-oriented instabilities [13]. Since it has lipophilic properties, Curcumin has practical insolubility while in an aqueous medium or solution at a neutral pH and room temperature [14]. As such, these limitations necessitate the application of organic solvents like ethanol, dimethyl sulfoxide, methanol, or acetone to enable its convenient use as a treatment remedy against peripheral neuropathies [15]. Furthermore, Curcumin has relative instability. It portrays a quick degradation into different compounds like feruloyl, vanillin, methane, autoxidation products (especially bicyclopentadione), ferulic acid while at an alkaline or neutral pH [1]. Additionally, Curcumin also has light sensitivity in both solubilized and solid forms [16].

Increased Metabolism of Curcumin

Multiple sets of research studies have been conducted in human beings regarding the metabolism of Curcumin. These, in particular, include the homogenates of liver tissue or those of microsome fractions of intestines. The studies assert that the metabolism of Curcumin majorly occurs via reduction and subsequently conjugation [3]. The primary degradation products that emerge from reduction, which majorly happens via the influence of alcohol dehydrogenase, are octahydrocurcumin, tetrahydrocurcumin, dihydrocurcumin, and hexahydrocurcumin[Figure 3] [17]. The second phase of metabolism, whose occurrence initiates through sulfonation/glucuronidation conjugation, readily conjugates Curcumin plus its decreased metabolites [2]. As a consequence, only little and insignificant magnitudes of Curcumin get to be absorbed by the body and are in turn present in ~~the~~ blood as sulfate metabolites and glucuronide [18].

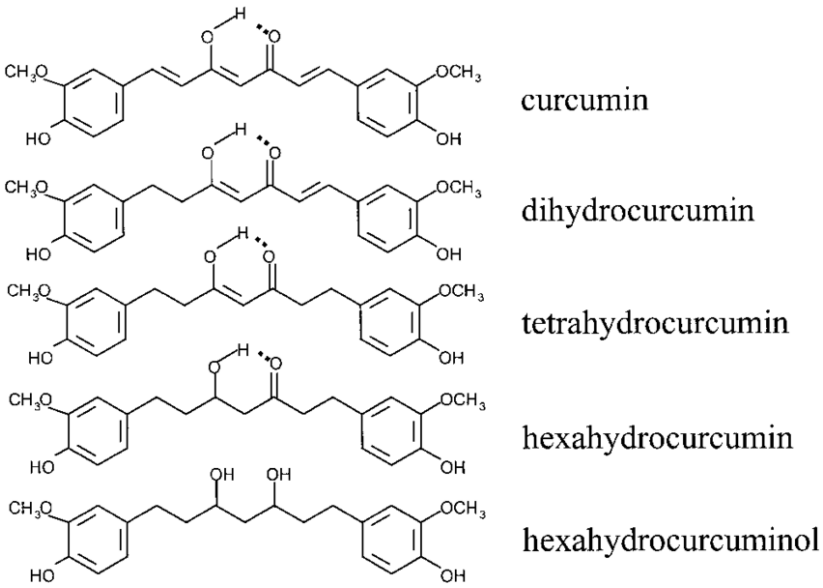

Figure 3: Products of Metabolic Curcumin Reduction [16].

Loss of Sensitivity during Curcumin Administration

Some peripheral neuropathies do not yield pain. However, on the contrary, they present a loss of sensitivity. The fact is more probable in pathologies of traumatic origin (nerve transection and crushing) or genetic origin pathologies (for instance, the CMT) [19]. In such cases, sensory nerve fibers loss substantially results in the loss of sensitivity. Curcumin, due to its effects related to neuro-protection, has proved to boost thermal and mechanical sensitivity in sciatic nerve crushing models. The loss and regain of body sensitivity, however, depends on the amount of Curcumin administered during the process of treatment in the peripheral nerve regeneration in sciatic nerve injury.

Peripheral Nerve Regeneration Uncertainties

Curcumin has the capability of boosting the regeneration of peripheral nerves in normal conditions. However, it is uncertain whether its beneficial health effects on nerve regeneration still exist under diabetes (Mellitus). Some of the contemporary research studies were meant to aid the investigation of such ~~as a~~possibilities. For instance, some research studies had diabetes developed in rats through applying streptozotocin (50 mg/kg) in a single dose [1]. The diabetic rats were then administered with Curcumin in doses of 50, 100, and 300mg/kg daily (intraperitoneally) from a period of 4 weeks after the nerve crush injury or with normal saline [17]. The regeneration of axons had to be investigated by retrograde labeling and morphometric analysis. There was then an evaluation of recovery of function by analysis of behavior and electrophysiological studies. Curcumin significantly enhanced the recovery of

functions and the regeneration of axons and was potentially better than the ones in saline group vehicles. Additionally, extreme curcumin doses (100 and 300mg/kg) achieved improved recovery of functions and regeneration of axons better than the 50mg/kg dose [1]. Therefore, Curcumin has the capability of promoting the regeneration of nerves after the sciatic nerve injury in the state of diabetes mellitus and also highlights its therapeutic benefits as an agent of neuroprotection for the repair of peripherally-associated nerve injury in diabetes mellitus.

Chemotherapy-Induced Curcumin Peripheral Neuropathy

Applying various anticancer agents such as taxanes, vinca alkaloids, cisplatin, and oxaliplatin (platinum drugs), among other related chemotherapeutic drug interventions in cancer treatment, results in Chemotherapy-Induced Peripheral Neuropathy (CIPN) and affects 30 to 40% of patients [1]. CIPN-related symptoms begin with the trigger of chemotherapy and register an improvement with the completion of the therapy. However, nearly 25 to 30% of patients undergo unpleasant paresthesia or pain, which even does not easily end after the completion of chemotherapy [3]. Additionally, CIPN has the potential of resulting in a reduction in the chemotherapeutic doses, which cause treatment cessation, and even reflect less effective health results [13]. Concerning cellular mechanisms,vincristine, paclitaxel anticancer drugs, and oxaliplatin result in mitochondrial rapturing of the sensory neurons located within the Dorsal Root Ganglion (DRG), creating an elevated secretion of the ROS [20]. Chemotherapy triggers the impairment of cellular respiration and lowers the secretion of Adenosine Triphosphate (ATP) [21]. As such, the restoration of mitochondrial bioenergetics and promotion of mitochondrial respiration offer protection against CIPN [14]. Moreover, offering treatment using anticancer drugs results in the decrease of ~~an~~ antioxidative enzyme like the Catalase (CAT) and Superoxide Dismutase (SOD), leading to the imbalance of antioxidants and oxidant molecules [22]. The resultant imbalance propels the promotion of the pathways (apoptotic cellular pathways), which leads to peripheral sensory fiber degeneration and other occurrences which are inflammatory [23]. However, antioxidant qualifies as the most reliable and appropriate treatment for CIPN [1]. Chemical Structures of Clinical and Pre-clinical Formulations of Curcumin as applied in Peripheral Neuropathies were shown in Figure 4.

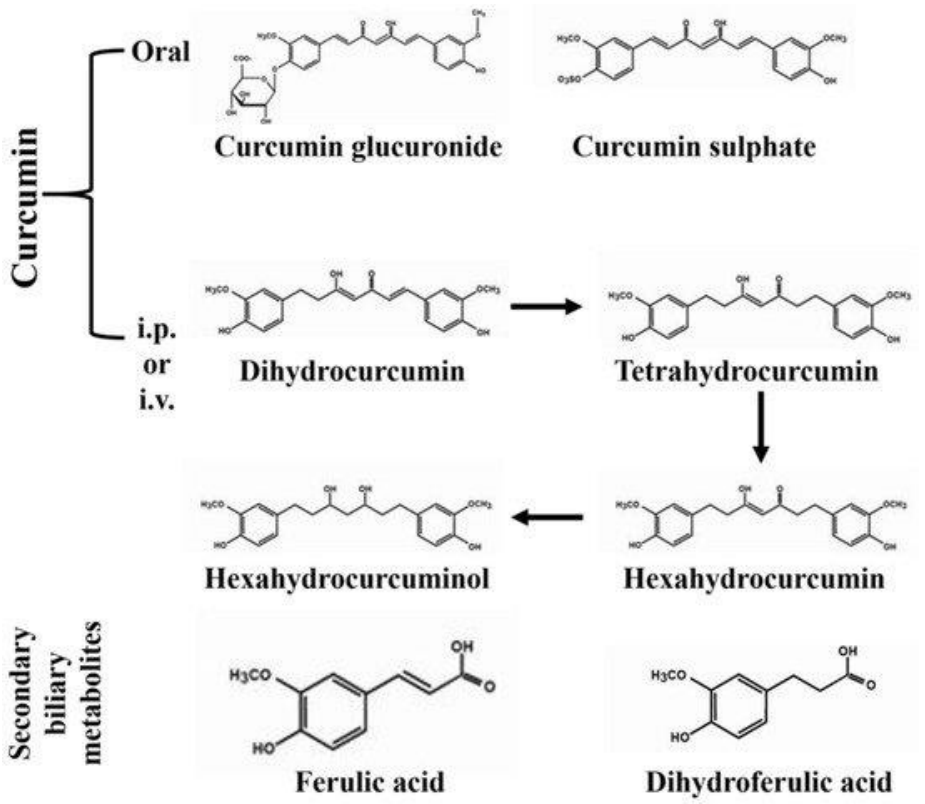

Figure 4: Chemical Structures of Clinical and Pre-clinical Formulations of Curcumin as applied in Peripheral Neuropathies [1].

Alcoholic Curcumin Neuropathy

Consumption of alcohol chronically results in a series of neurological-related aberrations such as delirium tremens, motility, and cortical dysfunction, peripheral polyneuropathy, Wernicke encephalopathy, and psychosis[Figure 5] [24]. Alcoholism in the history of a family, direct exposure to alcoholic toxicity, thiamine deficiency, malnutrition associates closely with alcoholic neuropathy [20]. However, there are uncertainties regarding which specific factor of factors among the ones presented above links to the inducing neuropathy [11]. Furthermore, alcohol boosts oxidative stress by reducing the antioxidants' endogenous concentrations like vitamin E, ascorbate, α-tocopherol, generating lipid and ROS, and rapturing the DNA, cellular protein, and other pathways of signals that limit oxidative stress [7].

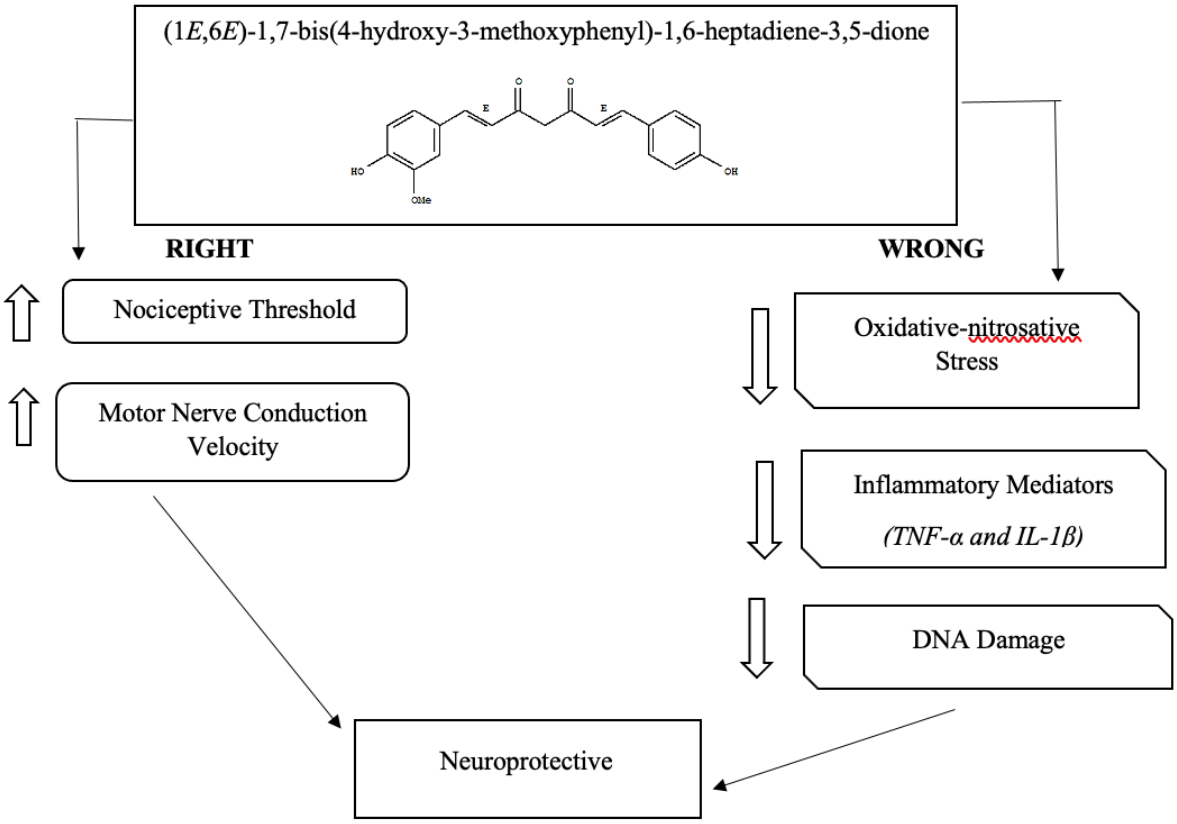

Figure 5: Alcoholic Chemical Simulation of Curcumin Neuropathy [24].

Curcumin Postoperative Pain

Despite the effectiveness and reliability of adopting Curcumin as the best alternative in its treatment effects, particularly as an anti-inflammatory activity in peripheral nerve regeneration in sciatic nerve injury, patients still experience postoperative pains. The patients' perception regarding postoperative pain is that it is among the known noxiously severe surgical pain aspects which lack the most effective and reliable control measures [9]. As per the many proven instances of acute treatment in peripheral nerve regeneration in sciatic nerve injury, Curcumin has demonstrated activity of anti-hyperalgesia through dependently reversing it via dosages, whereas recurrent treatment procedures facilitate the postoperative pain recovery [12]. However, implementing Curcumin in repeated treatment instances before surgery does not reflect any input concerning reducing or preventing postoperative pain [13].

Although Curcumin does not leadto the alteration of anti- and pro-inflammatory cytokines during the peri incisional stage, it augments the transformation of growth factor-β (TGF-β), whose implication inhibits nociception in both neuropathic and inflammatory pain models[25]. Importantinsights concerning the mechanisms underlying Curcumin's antinociceptive action in postoperative pain reveal some facts. The antagonization of the receptors of gamma-aminobutyric acid (GABA) abrogates the curcumin-initiated activity of the anti-hyperalgesia, and the mRNA expression of GABA-B and GABA-A in the incision of the spinal cord elevates from the curcumin treatment. [1] On the other hand, the antagonization of the opioid receptors reverses the action of Curcumin's anti-hyperalgesia but does not change opioid receptors' mRNA expression in the spinal cord [26]. The fact indicates that opioid receptors have indirect engagement in the mediation of curcumin antinociception of sciatic nerve injury and other forms of postoperative pains.

Conclusion and Recommendation

Generally, peripheral nerve regeneration in sciatic nerve injury has many treatment remedies. The common ones are the First-, Second, and Third-line treatment drugs. However, the application of these drugs characterizes ~~by~~ some negative effects. Therefore, better therapeutics should be obtained, particularly those with limited to no post-treatment (post-surgery) pain consequences, besides their improved efficacy. The fact, therefore, presents the option of Curcumin. There should be an establishment of Curcumin formulations with minimal to no post-surgery pains and aftermath of Curcumin-related health complications. As a polyphenol generated from the Curcuma longa roots, Curcumin has anti-inflammatory, antioxidant, and antibacterial medical traits. The adoption of Curcumin presents a faster rate of metabolism and reduced bioavailability, both of which have resulted in the establishment of different formulations of Curcumin. These properties, therefore, do not offer 100% reliability curcumin as a remedy but make it assume some disadvantages during its administration unto the patients. The need to implement Curcumin and its associated formulations as medical remedies to postoperative and neuropathic pains elevates the significance of comprehensive analyses of their effects regarding their reliability to perfectly execute such health functions. According to the positive results generated from the related medical researches, Curcumin presents a quite beneficial degree of reliability as a remedy or health remedy appropriate in the prevention of postoperative and neuropathic pain conditions.

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