Review

Curcumin and Its Affection for Sleep Deprivation

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Abstract: In this review, the following information describes the manifestation of sleep deprivation by human beings and its adverse effect on their health. Sleep deprivation has been demonstrated into namely two types known as REM sleep and NREM sleep affecting our health in so a problematic way that it is making our body immune to many diseases leading to lethal problems. Therefore, great research by many scientists has discovered that the turmeric *"Curcuma longa"* which is been used in every Indian kitchen since ancient times, has shown a remarkable effect on the problem caused by sleep deprivation but due to its poor solubility and low bioavailability drawn it into a great disadvantage. But the help of the study of nanotechnology and the evolution of curcumin into nano–curcumin made the possibility of the remarkable effect by making the curcumin more potent and enhancing its stability. Immunological changes due to sleep deprivation lead to Alzheimer's disease, glioma, neuropathic pains, and many more. Therefore, this review has been summarized as it is been providing information related to curcumin and its affection for sleep deprivation.

Keywords: Sleep deprivation; Cytokines; curcumin; nano – curcumin

1. Introduction

Sleep is recognized as one of the important phases of our body function which is required by all living organisms on this earth. It is of two types known as Rapid Eye Movement Sleep (REM Sleep) and Non–Rapid Eye Movement (NREM) for the maintenance of statical behavior of mental and physiological structure of a living organism. Lack of sleep leads to many different acute and chronic diseases such as premature death, brain excitability, arthritis, Alzheimer's, and Parkinson's disease with adverse effects of irritability, anxiety, confusion, and so on, in humans as well as in animals.[1] As studies suggest increased daytime sleep leads to narcolepsy with REM sleep, hypnagogic hallucination, and sleep paralysis. Due to this sleep wake-pattern disturbances and improper hypocretin increases the percentage of inflammatory

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cytokines (TNF-α-1, IL-1, IL-6) during the day as a part of sleep regulation. The rising level of BMI and proinflammatory cytokines levels and narcoleptic symptoms can be caused by TNF-α-1 and the relationship between IL-6 (augment fatigue and sleepiness) with narcoleptics disturbances in metabolites of food due to depleted hypocretin as IL-6 because it is one of the factors who also leads to obesity. *Hinge-Selch (1998)* assessed cytokines levels of IL-1β, IL-1ra, IL-2, IL-6, TNF-α, and TNF-β in plasma and nitrogen stimulated monocytes and lymphocytes in narcoleptics and HCA and watched their controls, where it's been found only IL-6 has been secreted but having the negative result for the secretion of T-Cells abnormalities. Animal data it's showing the strong implication in the relationship between proinflammatory cytokines (IL-1, TNF-α-1, and IL-6 and sleep modulation) where TNF and IL-1 are somnogenic in NREM in rats. It is been found that IL-6 is occurred mainly during the period of illness but is also found alternatively in the condition of NREM in rats and humans. With the collected data it can be implicated as at stages 1 and 2 of REM sleep the IL-6 is secreted, and the elevation of TNF-α and hGH secretion as SWS wing a possible alteration in hGH levels for narcoleptics.[2] As REM sleep leads to neurogenesis, modification of neurochemical and hormonal milieu also induces plasma cortisol levels which leads to induce a stress response in REM sleep.[3] With the collected data study it has been found that the investigation related to REM sleep effects on different organs is very limited with one of the founding the effect on the liver in mice related to REM sleep with effects of curcumin to these experimented mice giving very effective results, can also lead to with the hypothesis effect of REM sleep on different organs and the effect of curcumin on other organs and with the discovery of more new drugs.[1].

1.1 A quick peek a glance at the particular principles of this review:

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Surveying different kinds of sleep-deprived research and review papers, I get to find out about the different types of its effects on our body. Where I have found that the research on sleep-related neurological bases topics and their effects were to be found in abundance but research related to their effects on different organs is in very few amounts.[1] Hence with keeping the following objectives as exploring immunological changes during rapid eye movement sleep (REM sleep), effects of nano–curcumin on REM sleep, exploring proinflammatory during REM sleep, and co-relation of immunomodulation with nano–curcumin during REM sleep the papers were searched.

Below are various studies that have been summarized regarding the same concept. As Atul Kumar Pandey et. al., 2011 reported in their research paper on research related to sleep deprivation, where he performed his experiment on male Wistar rats with the flowerpot method with the procedure like sample collection and immune transferase measurement, gel electrophoresis and densitometry, Edman sequencing and MALDI – TOF mass spectrophotometric analysis, RNA isolation and TaqMan real-time PCR, cytokines/ chemokines measurement and statical analysis were done with the result showing of the affected liver due to the release of AST and ALT due to ruptured hepatocytes which leads to the serious liver disease.[1] Following the second, M. L. Okun et. al., 2003 proposed exploring the cytokines and endocrine involvement in narcolepsy which is also one of the diseases caused by lack of sleepiness. Here, it's been introduced about narcolepsy which is due to the heavy amount of daytime sleepiness which is one of the symptoms of sleepiness along with the following – hypnagogic hallucination, sleep paralysis & catalepsy. Here, it is been addressed the possibility of the role of cytokines due to the improper function of the hypocretin level along with the might of the function of proinflammatory cytokines.[2] According to the paper of Ali Noorafshan et. al., 2017 it is been showing the study related effect of curcumin on REM sleep. Therefore, in this paper, it has researched of the following

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with the experiment and methodology where, it's been concluded with the following results - loss of body weight, along with loss of memory function, loss of volume of the CA1 and DG, loss of a total number of cells as compared with the curcumin-treated mouse there was no significant changes in body weight with the improved memory function, with increased volume percent of CA1 and DG and a total number of cells.[4]

2. Immunological changes, interrelation, and causes:

It's been assumed as the loss or lack of sleep weakens our body's defense system and gives an invitation to many diseases. It is also been studied that since the 19th century on animals like dogs lead to death due to sleep deprivation and the same studies related to mice have also been done which have also resulted in death within a few weeks due to the manifestation of REM sleep.[5] The sleep-wake cycles, emotion, and cognitive function is been regulated by the medial prefrontal cortex (mPFC) with the coordination of the hippocampus where which plays a key role in cognitive, mood, and memory.[6] It is been suggested for 7–8 hours of sleep for the proper regulation of metabolic homeostasis. REM and NREM generate improper immune function and disrupt the actual maintenance of proinflammatory cytokines such as Interleukin (IL – 6), Tumor Necrosis Factor (TNF – α) & C- reactive protein.[7] It has been shown that short rest length, low rest quality, and autonomic apprehensive brokenness are related to a few gamble factors for atherogenesis, including endocrinological, immunological, oxidative, fiery, and metabolic reactions, as well as endothelial brokenness.[8]

2.1 Flowchart presentation of the emergence of health issues related to sleep deprivation:

In figure 1, Influencing factors like duration and method of sleep deprivation, time points of specimen sampling, type of immune assay, the circadian system, analyzed species, environmental factors, age and health-related factors, psychosocial stress, and methods of sleep assessment. Research approaches for

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exploring rest invulnerable communications and potential affecting fac-pinnacles. Exploratory examinations research causal connections between rest and safe boundaries by manipulating rest or immunological variables.[5] Sleep is a crucial peculiarity and a sign of generally being well. Typical sleep is extremely fundamental for memory and cerebrum being well since different brain circuits in the mind are engaged with sleep. Lack of sleep has developed as a significant danger in present-day culture. SD hinders long-term protonation and particles related to memory and prompts mental brokenness. SD likewise hinders the leeway of harmful metabolites created in the cerebrum and adds to the pathophysiology of neurological problems like Promotion, Parkinson's disease, and cerebral stroke. SD additionally causes awkwardness in the resistant framework and exasperates the pathophysiology of Multiple - Sclerosis and glioma. It very well may be presumed that SD unfavorably influences different proteins, qualities, and sub-atomic fountains in neurodegenerative issues.[7]

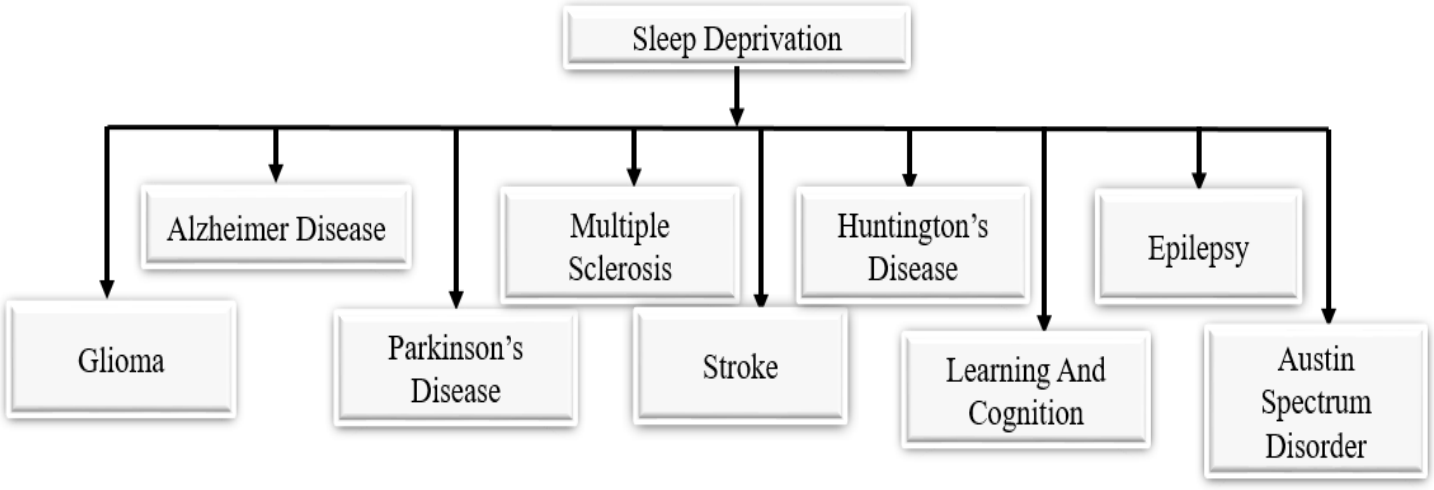

Figure: 1 Shows different kinds of sleep-deprived diseases caused due to the manifestation of REM sleep.

2.2 Interrelation between sleep and immunological responses:

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Nowadays sleep-related problems and disruptions to normal circadian regulation are common. With the following research, it's been also shown that circadian rhythms and sleep are correlated with the participation of immunological function to it.[9] Less sleep makes people tired and with low performance those people have 7 – 8 hours daily sleep. In studies, biological restraint of IL-1 furthermore, TNF has been displayed to diminish NREM sleep, and

height of IL-1 and TNF have been displayed to increment NREM sleep and lessen quick eye development (REM) sleep.[10] Under ordinary conditions, rest and the circadian mood guarantee a mitigating state during the daytime and a pro-inflammatory state during the evening.[9] Intense gentle resistant enactment increases NREM state of sleep and smothers REM state of sleep, though serious invulnerable reaction with an upsurge of cytokine levels causes rest aggravation with the concealment of both NREM and REM state of sleep.[11]

Luísa de Sousa Nogueira Freitas et.al., 2020 reported that in 2017 Watson explained about sleep and suggested TST between 9 and 10 required by the athletes for their recovery. With some more explanation, it is been demonstrated that sleep plays a vital role in protein synthesis and protein degradation. It was found that sufficient rest decreased these numbers when contrasted with aggregate and fractional lack of sleep. It was found that adequate rest diminished these numbers when stood out from the total and fragmentary absence of rest.[12][9] The circulating immune cells and their cytokines production is been affected by sleep. Where it is been informed that nocturnal sleep number down the leukocytes in blood & increase their number in lymphatic tissues. With sleep, it's been said that IL – 2 is the T-cell derivation or another type 1 cytokines supporting the adaptive immune defense.[13] The influence of physical performance on the recovery of strenuous activity is been established by sleep. In addition to the reduction of sleep, it also has a severe negative impact on skeleton muscle with hormone imbalance and cytokines. Where it is been also introduced that an

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increased level of AST, ALT, and LDH are makers of muscle damage due to sleep affect.[12][1] In figure 2, the following flow chart is showing the short rest span and low rest quality, alongside resultant autonomic anxious brokenness that might instigate movement of atherosclerosis, possibly through endocrinological, immunological, provocative, and oxidative reaction, and endothelial brokenness.[8]

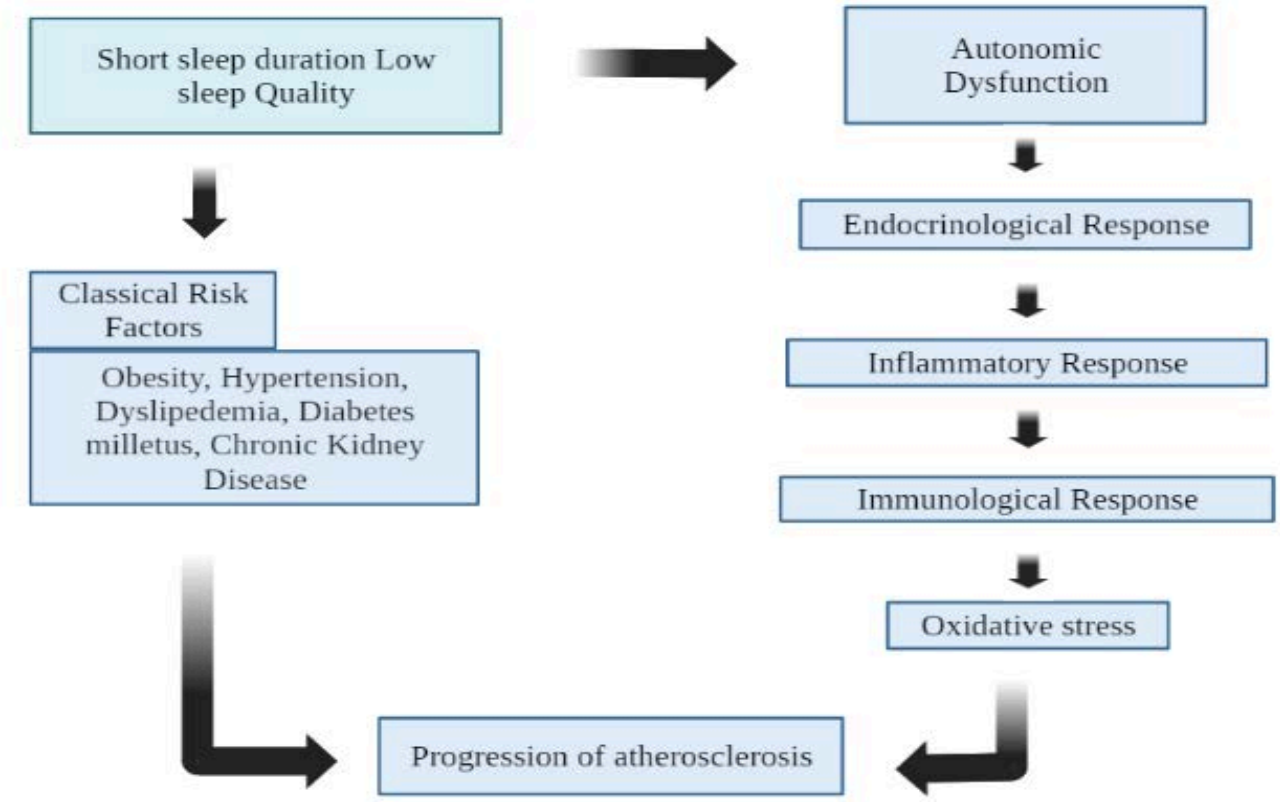

Figure 2. Mechanisms associated with short sleep duration and low sleep quality with which it leads to classical factor along with autonomic dysfunction ending with the progression of atherosclerosis.

In the next figure 3, the flow chart is showing the athlete could reduce the testosterone and GH, which encourages the reduction of PI3K activation, and according to which phosphorylation of Akt decline, which switches off the mTOR signaling, damaging the S6K1 and Bmal activation. It also reduces HSPs and makes rises of ROS, and addition of cortisol levels which hinder IGF- 1 secretion. Accordingly, the loss of IGF – 1 grows PI3K deactivation and instigates REDD – 1 4EBP1 and FOXO activation. The rest obligation could

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disable the sphingolipids morphology on the cell layer, prompting an unsettling influence of incendiary guidelines, including expanded degrees of IL-6; IL-1β; TNF-α, enactment of prostaglandins, and ubiquitination processes. Other than that, IL-10; AnxA1; LXA4, RvE, and RvD levels are motioned toward being decreased. The effect of sphingolipids add to diminish IGF-1 discharge, supporting the pathways recently depicted and also, moreover, decreasing insulin awareness. The outcome of the unsettling influence on cell flagging is a decrease in protein combination and muscle recovery, and a high gamble of outer muscle injury. Legend: GH: development chemical, PI3K: phosphatidylinositol-3 kinase, p-Akt: phosphorikated protein kinase B, mTOR: the mammalian objective of rapamycin, S6K1: Ribosomal Protein S6 Kinase 1, HSPs: heat shock proteins, ROS: receptive oxygen species, IGF-I: insulin-like development factor I, REDD1: managed being developed and DNA harm reactions 1, 4EBP1: eukaryotic interpretation commencement factor 4-E restricting protein 1, FOXO: forkhead record factor, IL-6: Interleukin 6, IL-1ß: Interleukin 1 beta, TNFα: cancer putrefaction factor alpha, IL-10: Interleukin-10, AnxA1: Annexin A1, LXA4: Lipoxin A4, RvE: resolvin E, RvD: resolvin D.[12]

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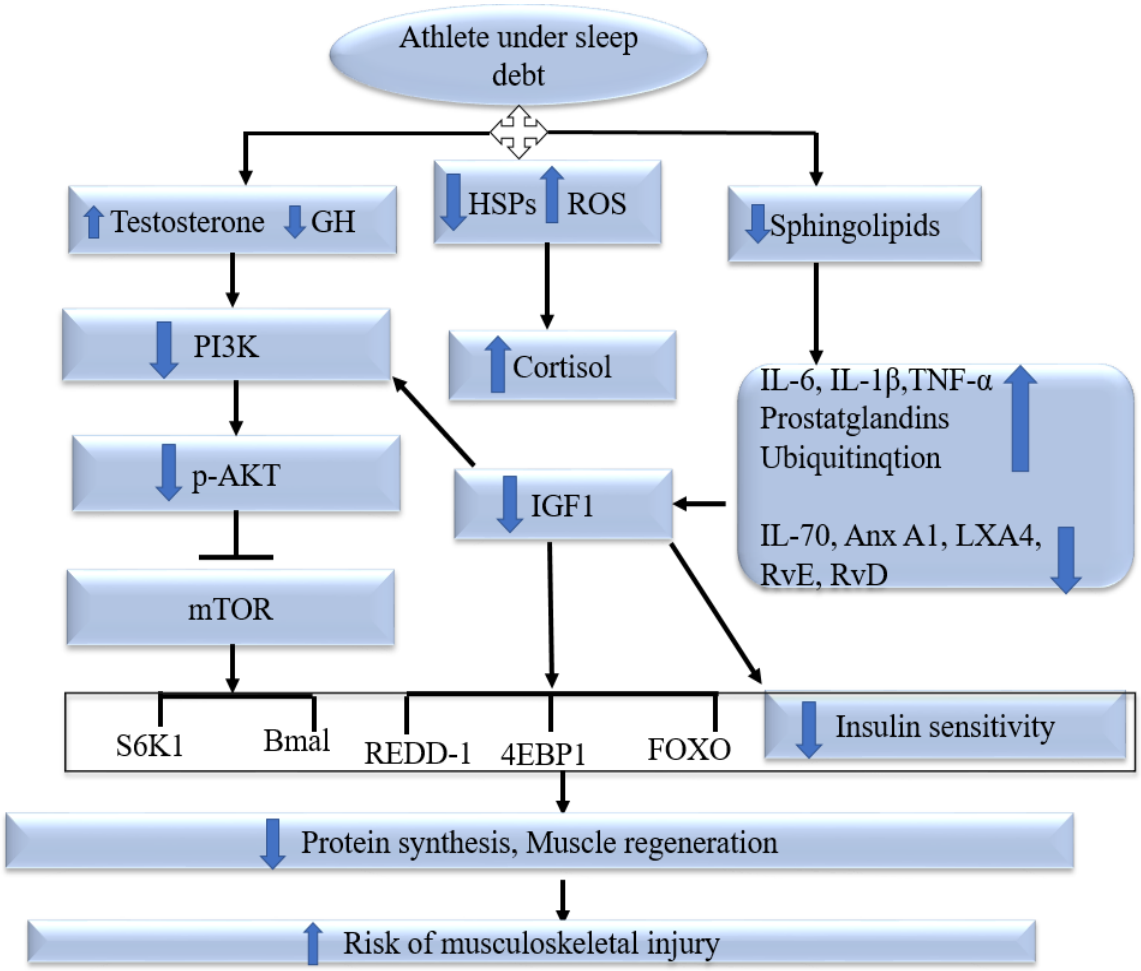

Figure 3. The system proposed for the expanded occurrence of outer muscle wounds in competitors with sleep obligation shows results with decreasing protein making and muscle generation and with the increment risk of muscle injury not letting them be cured within the normal period.

3. Effect of nano–curcumin on REM sleep

The plant has its history related to medical use for human welfare, where the use of herbal plants for medicine purpose has also attracted the worldwide.[14][15] Curcumin is the extraction of gingeraceae turmeric from the rhizome and is a fat-soluble polyphenolic pigment. Many studies along with research have shown a great result of a great effect of curcumin for health purposes with fabulous effect such as antioxidative stress, anti-apoptosis, and anti-inflammation along with plays a vital role in molecular targets of multiple pathways hence, protecting numerous organs activity.[16] If we turn on pages of history we will be able to find out about the great importance of turmeric in Ayurveda in the religion of Hinduism.[14] Curcumin has

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shown a remarkable biological action as a growth enhancer along with antiparasitic effects, hepatoprotective, bactericidal, and antioxidants.[15]

4.1. Significance of action of curcumin on different parts of the body:

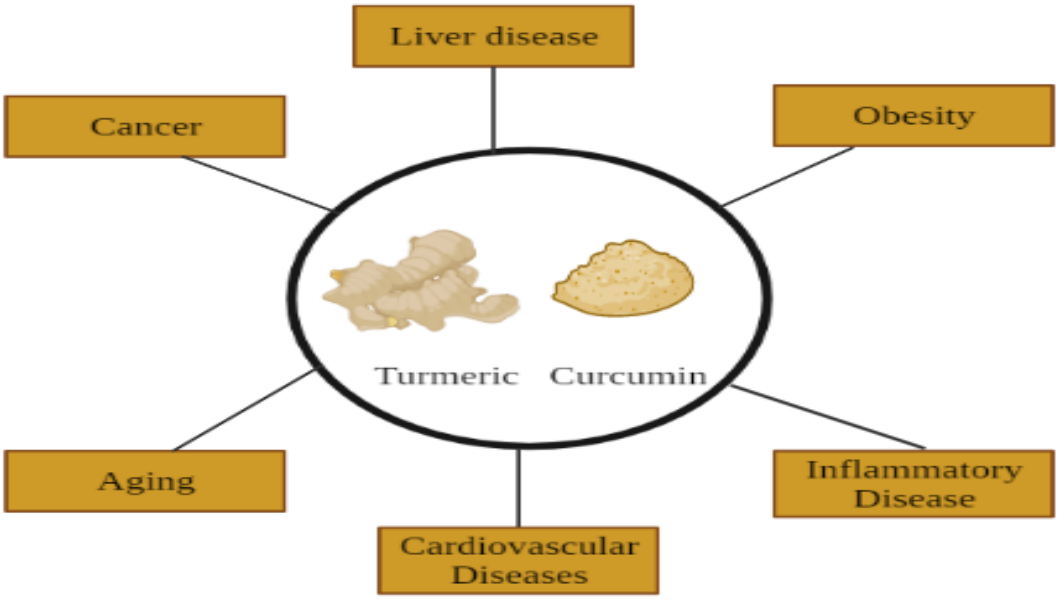

Figure 4. Application of curcumin in the treatment of different illnesses.

Curcumin has been used for millennia as a wound-healing agent and for treating a variety of diseases in traditional Indian and Chinese medicine.[17] In above figure 4, Curcumin is for the most part utilized as a zest, and what's more, a food-shading specialist in Southeastern Asian cooking. Curcumin, a characteristic compound detached from C. longa, has numerous applications in the treatment of different illnesses such as cardiovascular infections, liver illness, corpulence, malignant growth, fiery sicknesses, and maturing.[14]

4.2. Significance of curcumin on REM sleep with the explanation of relationship among ROS:

Because of its potent antioxidant and anti-inflammatory, curcumin is predicted to be a neuroprotective agent.[14] It’s been accounted that sleep deprivation increased free radicles and drop down the oxidative defense by disturbing the balance between oxidative and antioxidative defense.[18] Lack of sleep (SD) is known to bring about a scope of neurological outcomes in persistently distressing subjects.[19] The research

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has shown that the disturbed sleep-wake cycle (SD) has generated a DNA desecration response and neuronal death, crushing the neuronal augmentation, and decreasing the hippocampal gliogenesis and dendritic spines and length in different parts of the brain.[20] Sleep deprivation has known to be a destroyer of a variety of brain malfunctions, along with the reason of improper function of memory, depression, and psychosis.[19] Turmeric divides itself into three parts as known as far as curcumin, demethoxycurcumin, and in bisdemethoxycurcumin controlling the effect of inflammation, cell growth, and apoptosis. Property of antioxidant and anti-inflammatory curcumin helps in the treatment of many diseases.[21] Where factors of oxidative stress and oxidative damage leading to chronic inflammatory and degenerative leading to a variety of diseases like cancer, atherosclerosis, and Alzheimer's disease with a metabolic disorder. The given below with figure 5, in which it shows the process of persistent oxidative stress which can lead to chronic inflammation.[17] The factor of oxidative stress leads to disturbances in the balance between the production of ROS (free radicles and reactive metabolites) and antioxidant defenses, which is one important factor in degrading biomolecules and cells. Hence, ROS act as the center for the both upstream and downstream NF – kβ and TNF – α pathways and where hydroxyl radicles are the most harmful of all the ROS. [22][23]

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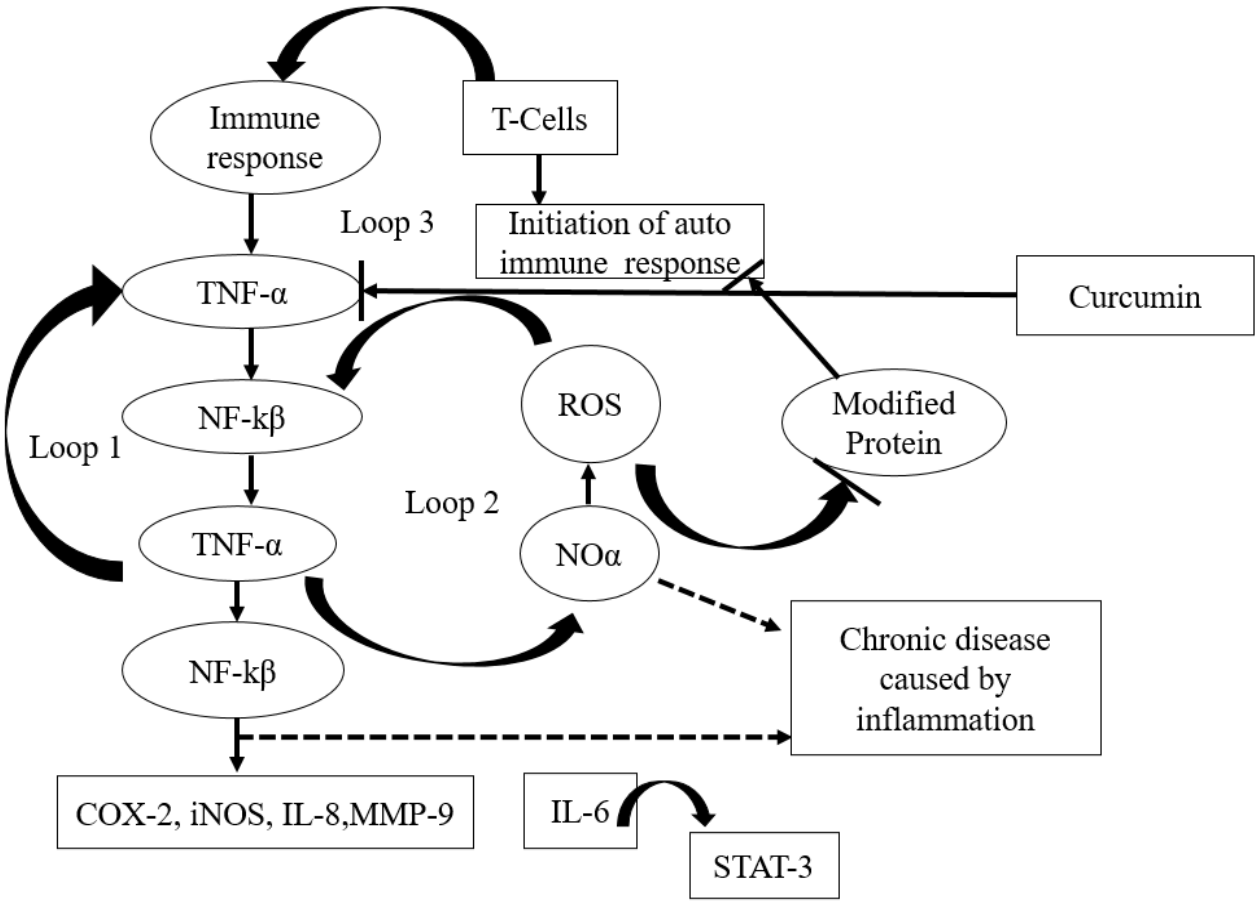

Figure 5. Relationship among ROS with the different three loops, persistent irritation illnesses, and the antioxidative properties of curcumin.

4.3 Action of nano–curcumin on REM sleep:

With the amazing action of curcumin in the biological and pharmacological area, it has attracted attention but its poor bioavailability, and low solubility makes it to drag into a major disadvantage. Therefore, nano–curcumin has made up for the possibility and enhanced the biological and pharmacological benefits of curcumin.[24] Where, Mehdi Maghbooli et. al., 2019 have discussed that nanomicelle curcumin significantly increased sleep quality and QoL in patients with PD compared to the placebo group.[25] On the other hand, Yang has introduced references that curcumin could work on the brain recovery of rodents' hippocampus.[26] Additionally, Issuriya affirmed that curcumin forestalled cell misfortune achieved by dexamethasone in

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rodents' hippocampus. Albeit the component by which curcumin forestalls memory disability and primary changes of the hippocampus and DG requires further examination, curcumin could apply its belongings through alienating oxidative pressure in the hippocampus and additionally DG. In light of our outcomes, REM-SD might actuate impedances in spatial memory and the design of the hippocampus. Many investigations have exhibited that book object acknowledgment can be hippocampus-reliant or autonomous which appears to rely upon the convention utilized. All things considered, it isn't clear if changes in hippocampal volume connect with the exhibition in the errand.[18][27][28][29][30][19][4]

4. To explore proinflammatory cytokines during REM sleep

Since the 1970s, prerequisite studies have demonstrated that there is a strong relationship between the poor quality of sleep with psychological factors, especially in the content of deem stress.[31] Proinflammatory cytokines will be cytokines delivered overwhelmingly by enacted insusceptible cells, like microglia, furthermore, are associated with initiating the amplification of inflammatory responses, for the most part, the intense stage response. These cytokines incorporate IL-1β, IL-1, IL-6, TNF-α, and IL-17.[3] In addition, increments of the inflammatory marker, C-receptive protein (CRP), tentatively foresee weakness in the local area staying in grown-ups. Taken together, these discoveries recommend that irritation and changes in sleep might add to weakness or potentially decreases essentialness.[32] Atul Kumar Pandey et. al., 2011 explained in their paper, that the degree of favorable to incendiary cytokines like IL-1b, IL-6, and IL-12 (p70) expanded altogether when contrasted with the controls on the fourth as well as the ninth day of REMSD. Cytokines, the key couriers of the fringe resistant framework not just manage the declaration of intense stage reaction proteins, including A1I3 yet, in addition, adjust sleep. Complete sleep misfortune prompted expanded degrees of fiery cytokines IL1-b and IL-6. This is predictable with past reports that IL-6 is the central middle person of APR, while IL-1b has a restricted direct job and is generally interceded through IL-6.[1] Initiating the adaptive immune response. The attacking antigen is taken up and handled by antigen introducing cells (APC) which present sections of the antigen to T assistant (Th) cells, with the two sorts of cells framing an ‘immunological neural connection’. The accompanying arrival of interleukin (IL)- 12 by APC instigates a Th1 reaction that upholds the capability of antigen-specific cytotoxic T cells and starts the development of antibodies by B cells.

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This reaction at last creates dependable immunological memory for the antigen. Rest, specifically sluggish wave rest (SWS), what's more, the circadian framework act how to create a favorable to fiery hormonal milieu with upgraded development chemical and prolactin discharge as well as decreased levels of the calming pressure chemical cortisol. The hormonal changes thus support the early strides in the age of a versatile safe reaction in the lymph hubs. In similarity to neurobehavioral memory framed in the focal apprehensive framework, the various periods of immunological memory may be isolated in encoding, solidification, and a review stage. In both the focal sensory system and the safe framework, the rest explicitly upholds the union phase of the particular memory types. Adjusted from Lange and Born.[33]

5. Discussion

Sleep is seen as one of the important phases of our body function containing two mainly two types namely (i) REM sleep and (ii) NREM sleep.[1] A diet routine poor in tryptophan seems to hinder rest. Intense tryptophan exhaustion influences the combination of serotonin and can diminish REM sleep beginning dormancy in ordinary sleepers.[34] Lack of sleep initiates nerve center pituitary-adrenal (HPA) pivot and impact a few natural impacts at both focal and fringe level.[18] With the influence of inflammatory and pro-inflammatory cytokines due to manifestation of REM sleep and due to the disturbance of sleep-wake cycle.[2] REM lack of sleep initiates weight reduction, displaying a condition of expanded energy use.[20] Lack of sleep has been accounted for to cause hypermetabolism which brings about weight reduction despite expanded food admission.[18] The circadian musicality and related arrival of cortisol and epinephrine on rhythms and rearrangement of leukocyte subsets. Rest contrasted and nighttime alertness upgrades the homing of gullible T aide (Th) cells to lymph hubs which prompts marginally diminished quantities of these phones flowing in blood during rest. The systems of this upgraded homing of cells during rest are not perceived. During daytime attentiveness, the circadian ascent in cortisol actuates an expansion in CXCR4 articulation on undifferentiated or less separated leukocytes, like gullible Th cells, which thusly empowers the reallocation of these cells deep down the marrow. Then again, epinephrine controls the musicality of exceptionally separated leukocytes, as cytotoxic regular executioner (NK) cells, going about as effector cells. During daytime alertness, the upgraded initiation of β2-adrenoceptors by epinephrine lessens CX3CR1/CD11a flagging, which prompts an improved assembly of proposals cells from the peripheral pool during daytime. Decreased epinephrine levels during rest (contrasted with nighttime attentiveness) permit the margination of these cells, which brings about lower cell

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numbers in fringe blood.[33] Additionally, curcumin has shown a great impact with its curing property as a potent antioxidant and anti-inflammatory property.[14] Curcumin as an endogenous dynamic protein, HO-1 is broadly conveyed in harmed organs and assumes a part in safeguarding tissues and organs through numerous components like antioxidation, hostile to irritation, and anti-apoptosis.[16] Curcumin expanded the exercises of the proteins situated at the stomach brush line answerable for supplement debasement and absorption, in this manner working on supplement accessibility and development.[15] But its poor bioavailability and low solubility property have given it major disadvantage criteria where, with the introduction of nano–curcumin surpassed this low bioavailability and poor solubility property of curcumin and has shown tremendous effects on SD with its nice stability.[24] It is the obvious reason that curcumin bioavailability is too lower. To eliminate this issue, new details, for example, nano - curcumin are created. The Discovery of nanoformulations is a restorative option in another revelation stage, being nontoxic for other body cells.[35] With the following data, it is been discussed that nitric oxide balance was ensnared in the protective effect of curcumin in improving conduct changes also, oxidative harm actuated by intense sleep deprivation.[4]

6. Conclusion

Clinical examinations showed the low bioavailability of curcumin; subsequently, in low dosages, no action was seen in patients. To conquer this issue, new definitions with different organization courses ought to be created.[14] It’s been announced that the spatial game plan of SCG neurons in the CSD creatures changed into an irregular example, and utilizing curcumin saved its dissemination like the typical design in the customary one.[20] Curcumin can likewise increment intracellular glutathione levels by keeping up with the action of histone acetyltransferase in monocytes in this way moderating harm during oxidative pressure.[16] Restraint of hippocampal cell misfortune or advancement of neuronal expansion in the brain is a promising technique for PD treatment. Moreover, several recent reports propose that the neuroprotective job of curcumin is useful from a decrease of cadmium-incited cytotoxicity. [26] Concentrates on the natural assessment of curcumin have uncovered that curcumin is supportive of medication, which represses the development of cells by delivering dynamic free thiol bunch inside the objective site.[36]

7. Abbreviation

1. **REM –** Random eye movement
2. **NREM –** Non-random eye movement

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3. **TNF – α –** Tumor necrosis factor-alpha
4. **IL –** Interleukins
5. **BMI –** Body mass index
6. **HCA -** Hemocyte Cytotoxic Activity
7. **hGH –** Human growth hormone
8. **SWS –** Slow-wave sleep
9. **MALDI - TOF -** Matrix-assisted laser desorption ionization time-of-flight
10. **RNA –** Ribonucleic acid
11. **PCR –** Polymerase chain reaction
12. **AST –** Aspartate aminotransferase
13. **ALT -** Alanine transaminase
14. **CA1 -** Hippocampal cornu ammonis
15. **DG -** Dentate gyrus
16. **mPFC -** Medial prefrontal cortex
17. **TST -** Tail-suspension test
18. **LDH -** Lactate dehydrogenase
19. **GH –** Growth hormone
20. **PI3K -** Phosphatidylinositol-3 kinase
21. **p - Akt -** Phosphorikated protein kinase B
22. **mTOR -** Mammalian target of rapamycin
23. **S6K1 -** Ribosomal Protein S6 Kinase 1
24. **Bmal -** Brain and Muscle ARNT (Aryl hydrocarbon Receptor Nuclear Translocator)- Like Protein
25. **HSP –** Heat shock protein
26. **ROS -** Reactive oxygen species
27. **IGF –** Insulin-like growth factor
28. **REDD -** Regulated in development and DNA damage
29. **4EBP1 -** Eukaryotic translation initiation factor 4-E binding protein 1

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30. FOXO - Forkhead transcription factor

31. AnXA1 - Annexin A1

32. LXA4 - Lipoxin A4

33. RvE - Resolvin E

34. RvD - Resolvin D

35. NF – kβ - Nuclear factor kappa-light-chain-enhancer of activated B cells

36. APC – Antigen presenting cell

37. APR – Acute phase response

38. SCG - Superior cervical ganglion

39. CSD - Chronic sleep deprivation

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