



## REVIEW OF NUTRITION IN MALIGNANT PAIN – A PATHOPHYSIOLOGICAL APPROACH

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### Abstract:

The detection of malignancies is on the increase and with variable treatment modalities, they survive for more time. but the intriguing factor which breaks the quality of life is the pain associated with it. One quarter of all malignant patients suffer from intolerable pain. Numerous methods including pharmacological and non-pharmacological ways have been described to counter the agony. Nociceptive, neuropathic and psychogenic types of pain have been described in patients with cancer. Many nutrients have antinociceptive activity with anti tumour potential in a few. A proper balanced diet with adequate nutrients to combat pain can be more satisfying for the patients in pain. Fish oil with omega 3 acids, sitaphal, turmeric, chilli powder, milk with special ingredients to tackle pain have been described. A few of them exhibit anti neuropathic analgesic action also. Microbiota, essential amino acids are emerging new diet formula for malignant pain. No major side effects have been reported with intake of such analgesic and nutritious diet. We suggest that administration of nutritious analgesics should be a part of the management of malignant patients with pain. This is the first scientific attempt to bring different types of malignant pain and target them with specific nutritional supplements.

**Key words:** Pain, Cancer, Nociceptive, Neuropathic, Diet, Nutrition

### Introduction:

Cancer Pain (CP) is a multidimensional experience of pain which involves multiple neurophysiological changes. It is associated with significant cognitive, social, emotional and cultural responses. Moderate to severe pain is still being experienced by 40 to 50% of cancer patients: and an intolerable pain by 25 to 30% of such patients. The taxonomy of pain describes variable types of pain and all these varieties have been established with malignancies. The simple classification of pain are (1) Nociceptive which means that there is a noxious stimulus: this can be further divided into either somatic or visceral (a tumour invading the skin, muscles metastases to bone (somatic) or an organ (visceral) ) (2) Non nociceptive (absence of a noxious stimulus): may be peripheral, central or psychogenic. Innumerable pathophysiological changes develop in such patients and a many are not still decodable by the medical fraternity. The pain in malignancies are due to multiple causes. Multiple drug institution and selective nerve

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blocks have been described by the scientific community in terms of three step ladder. The world health organization has clearly demarcated patients suffering from malignant pain and suggested therapeutic measures. Many analgesics especially opioids used routinely have many side effects like nausea, vomiting respiratory depression etc. The simple analgesics like non-steroidal anti-inflammatory drugs are neither kidney nor stomach friendly. As there are different faces of cancer pain, the polypharmacy and their side effects are considered risky. It becomes a Hobson's choice to suffer from pain or the side effects of drugs. Hence, to look at the natural source to counter such intriguing problem of aching agony becomes mandatory. There are different types of nutrients and eatables which can counteract each of the mechanisms underlying pain in malignancies<sup>1,2</sup>. We will try to delineate each component of pain and explain how a nutrient can modulate such component.

### **Pathophysiology of malignant pain:**

Pain associated with different malignancies have differing etiologies. In a majority of cases (70% approx.) cancer pain is due to a direct involvement of the soft tissue, viscera, bone by the tumour cells and or due to a secondary structural change in the body (e.g., muscle spasm). In a few instances (25%) it may be due to the treatment<sup>3</sup>. This includes chemotherapy, radiotherapy, and/or surgery. Such pain is usually coexistent with associated psychospiritual distress. Peripheral and central sensitization phenomena have been also attributed to the genesis of malignant pain.

Peripheral pain mechanisms:

The initial growth of the tumour tissue and the surrounding destruction result in recruitment and infiltration of numerous inflammatory and immune cells such as mast cells, macrophages, and T-lymphocytes. This is basically a peripheral inflammation which subsides with drugs/nutrients with anti-inflammatory action. The role of nerve growth factor in peripheral sensitization have been described by stimulation of TRPV1 (Transient Receptor Potential Vanilloid 1) receptor<sup>4</sup>.

Central mechanisms:

Wide dynamic Range neurons exhibited an increase in spontaneous activity, and also an enhanced response to thermal and mechanical, stimuli applied to their receptive field. Although the mechanisms which promote central sensitization following tumour development are not known, it is possible that mitogen-activated protein kinases<sup>4</sup> may be involved. This ultimately results in hyperalgesia, allodynia and finally anaesthesia dolorosa.

Projections from the spinal cord initially run up to the thalamus and then to the cortex, providing information on the quality and the site of the stimulus. There is another pathway which supplies the limbic brain<sup>5</sup> and is the reason behind the affective components of pain.

### **Role of nutrients and diet:**

Emerging studies highlights a place for diet and nutrition as regulators in chronic pain<sup>6</sup> through the management of inflammation/ oxidative stress. There are a lot of nutrients



and dietary changes which can target the different pathophysiological changes and cause analgesia in such patients.

### **Fish oils: Omega 3 acids:**

The use of fish oil (in the form of cod liver oil), an omega-3 EFA, for the treatment of muscular, skeletal, and discogenic diseases, can be traced back to the late 18th century. Some examples of food high in omega-3 fatty acids include fish varieties like salmon, halibut and sardines. The other sources are walnut, flaxseed oil, and canola oil<sup>7</sup>. Maroon et al<sup>8</sup> have proved the anti-inflammatory action of omega 3 fatty acids and found to be useful in arthritis and discogenic pain. Tumour cells causing inflammation and pain as a part of nociceptive stimulus causing cancer pain can be effectively antagonized by omega 3 acids. Goldberg et al<sup>9</sup> have stressed the significance of alleviation of nociception with fish oils. They have used fish oil supplements in inflammatory arthritis and found them useful. An EPA-enriched supplement was reported to improve the tolerability of chemotherapy in patients with advanced colorectal cancer. Hence, combination of chemotherapy and omega-3 supplementation appears an effective combo strategy to better the clinical outcome of cancer patients. Neuropathic pain is a segment of malignant pain syndromes and a lot of studies have proved that fish oil supplements have diminished the neurogenic inflammation associated with such pain. Even though neuropathic component is being addressed by fish oils, the part seems to be relatively minor. Another study<sup>9</sup> has proved that these acids have a potential antidepressant effect. As cancer patients are prone for depressive illness such nutrient supplementation may help in addition to its antidepressant effects. The exact dosage, duration of intake of these nutrients has not been established. The cancer preventing action of omega 3 acids has been talked about but not established in trials. On the negative side of this nutrient, large doses of omega-3s > 6 gm/day has resulted in a fishy after-taste, and gastrointestinal disturbances and prolongation of prothrombin time<sup>10-14</sup>. As fish oil and walnuts are easily available in most parts of the world in affordable price, the intake of such nutrients can be easily recommended.

### **Sitaphal:**

Sitaphal or the custard apple is a fruit from the tree named *annona squamosa* which belongs to the family *Annonaceae* of the order *Magnoliales*. Even though leaves and bark extracts have been associated with antitumour activities, they can't be consumed as diet. The fruit by itself contains various chemicals including glycoside, alkaloid, steroid, terpenoid, flavonoid saponin and phenolic compounds. Other extracted chemicals include palmitone, organic acids and purines. Kaur et al in their studies have proved the extracts of sitaphal have demonstrable anti-nociceptive and anti-inflammatory activities to alleviate the suffering of cancer. One class of special chemicals which sets custard apple apart from other fruit species is the presence of acetogenins which has got anticancer activities and analgesic properties. Sitaphal kheer, cream, firni recipes<sup>15-17</sup> have been described.



### **Milk:**

Milk is the rich source of vitamin B12 and a few other nutrients. Even though milk has some analgesic effects and opioid sparing behavior, it has only been proved in rats. Milk is a rich source of tryptophan which induces regular sleep and decreases depressive symptoms which may be useful in cancer patients<sup>18</sup>. It is proven now that Vitamin B12 deficiency known for neurologic dysfunction and chronic pain. Mauro and colleagues, in their trial found that vitamin B12 injections<sup>19</sup> in non-deficient patients with pain resulted in decreased pain scores and analgesic use. There are a few studies which conclude that increased levels of B12 has been associated with higher cancer risk. Hence fish, milk and milk products as dietary supplements for cancer patients seems to be better option than therapeutic dosage in non-B12-deficient malignant patients. The researchers in a different study have tested the effect of nicotinamide riboside an ingredient of milk in female rats treated with paclitaxel have found analgesic effects<sup>20</sup>. Kynurenic acid from tryptophan is an NMDA antagonist and can be considered for modifying the transition to chronic pain from acute pain. Other than milk, potato is also a strong source of Kynurenic acid<sup>21</sup>. Supplementation of milk along with drugs has also been shown to decrease the neuropathic pain associated with chemotherapy. The most important advantage with milk is easiness to consume even with malignancies in the digestive system

**Turmeric and ginger** are related tubers have been studied for their anti-inflammatory properties. Terry and colleagues in their review concluded that ginger was a powerful anti-inflammatory and an effective analgesic<sup>22</sup>. Ginger functions as an anti-inflammatory by disrupting the cyclooxygenase 2 (COX-2) pathway at different targets. Being a natural product, curcumin of turmeric is non-toxic and inhibits multiple pathways involved in carcinogenesis and tumor formation. While the compound curcumin has shown some anti-tumor effects, the lack of significant systemic toxicity and multiple anticancer benefits may make it suitable as an adjuvant therapy for resistant head and neck cancers. The anti-inflammatory, antioxidant of Curcuma may be beneficial in the brain aging process but still studies are lacking about the beneficial effect of antiapoptotic in malignancies<sup>23</sup>. A few studies in breast cancer cell line have shown the beneficial effect of curcumin on tumor growth<sup>24</sup>. An average Indian diet may provide around 2,000–2,500 mg of turmeric (60–100 mg of curcumin) per day. Some recipes include, turmeric tea and turmeric milk<sup>25</sup>. Even though there are many herbal remedies for tackling neuropathic pain<sup>26</sup>, they don't form the paraphernalia of nutrition. Still ginger is essentially a nutrient consumed daily in the food has been proved to have properties to diminish the neuropathic component of pain syndromes.

### **Capsaicin or chilli pepper:**

Capsaicin is a natural vanilloid identified from various chili peppers. Even though both topical and oral preparations have found to be useful in neuropathic pain conditions, the usage is limited by its side effects of pungency and irritation. Hence alkaloid derivatives through its action on TRPV1 receptors can modulate pain due to different etiologies<sup>27</sup>.

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Still it's not extensively studied in chemotherapy induced neuropathic pain. Oral capsaicin has been used successfully in patients with cancer induced oral mucositis<sup>28</sup>. Otherwise capsaicin ointment is used to tackle neuropathic pain.

### **Essential amino acids and diet:**

The combination of chronic pain and opioid intake can cause deranged glucose metabolism in malignant patients. They have a desire to take primarily sugars and starches, with less protein or fat intake. The receptors to which pain-modulating neurotransmitters (eg. endorphin, serotonin, and GABA) attach are actually protein moieties<sup>29</sup>. The quantity of protein intake of patients with pain to provide enough amino acid substrate for producing pain-controlling compounds is yet not deciphered. A few examples of diet and essential amino acids are detailed below. Lysine in meat, eggs, soy, black beans, quinoa, and pumpkin seeds, histidine in Meat, fish, poultry, nuts, seeds, whole grains and threonine in wheat germ<sup>30</sup> are a few.

### **Miscellaneous:**

Spinach, onions, shallots, potatoes, black and green olives, globe artichoke heads, broccoli, asparagus, carrots are the rich source of polyphenols. These chemicals can have antioxidant, anti-inflammatory, antimicrobial, immunomodulatory, anticancer, vasodilating, and prebiotic-like properties<sup>30</sup>. Vaello et al<sup>31</sup> have described the anti-nociceptive effects (both somatic and visceral) of polyphenols. The same study has also revealed that polyphenols can effectively reduce neuropathic pain. Hence as the pain of malignancies is multifactorial, such combined polyphenol supplement in diet can help them in tackling such complex pain syndromes. Innumerable chemicals derived from food sources like Dehydrocorybulbine,  $\beta$ -Caryophyllene, Resveratrol, Palmitoylethanolamide, Zerumbone, vitamin D, Quercetin and berberine have been shown to decrease neuropathic pain<sup>32</sup>. Still anticancer potential has not been proven in these chemicals. The microbiome diet is a whole-food diet that focuses on consuming mostly fruit, vegetables, lean protein and a large amount of prebiotic and probiotic foods. Modulation of gut microbiota by diet and pharmabiotic intervention<sup>33</sup> offers a promising approach to the management of chronic pain. Gut microbiota modulation<sup>34</sup> is found to be very useful to alleviate the misery of chronic pain syndromes and particularly its associated depression. Different types of nutrients with combined actions on pain and cancer cells is pictured below. (fig.1)

### **Conclusion**

Strong evidences have come to support addition of nutritious diet to combat cancer pain. Simple addition of fruits and vegetables with a special eye on fish oils, milk and turmeric may be helpful in refractory cases. We suggest that administration of nutritious analgesics should be a part of the management of malignant patients with pain. Deciphering the taxonomy of cancer pain and targeting the specific derangement by nutritious supplements is to be explored.

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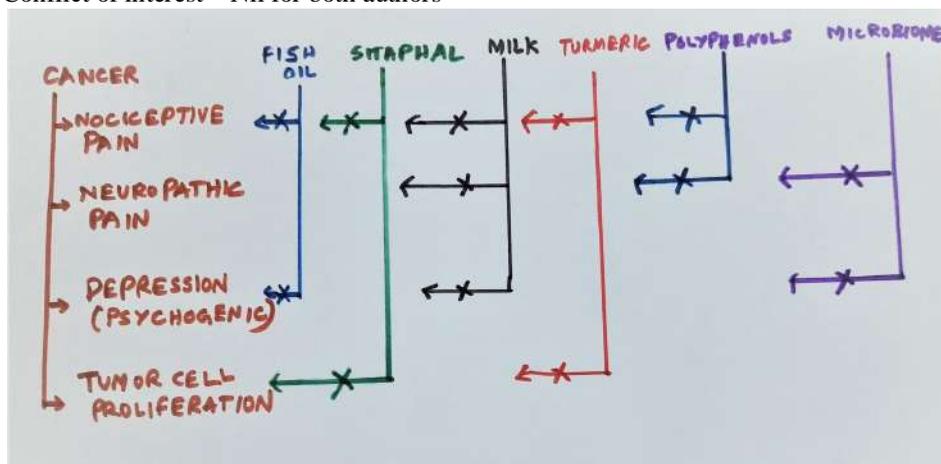


Figure 1 showing the nutrients and their possible actions

✕ = means counters