International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 506-522 www.ijprajournal.com ISSN: 2249-7781

Manage Your Esophageal Cancer by Nutritional Supplements: A Review

[1]Sakshi Deshpande, [2]Snehal Barve, [3]Tejaswini Deshmukh, [4]Kajal Gaykhe, [5]Dr. Dhanashri. R. Mali

[1,2,3,4]Student, Sir Dr. M. S. Gosavi College of Pharmaceutical Education and Research, Nashik, Maharashtra
[5]Assistant Professor, Department of Pharmaceutical Chemistry, Sir Dr. M. S. Gosavi College of Pharmaceutical Education and Research, Nashik, Maharashtra.

Submitted: 15-03-2024 Accepted: 27-03-2024

ABSTRACT: Esophageal carcinoma (EC) is one of the world's rare and deadly tumors. It has a high rate of metastasis and spreads through several channels. The two kinds of EC are squamous cell carcinoma (ESCC) and adenocarcinoma (EAC). Depending on their severity, endoscopy can diagnose them as T, N, or M. Dysphagia, GERD, indigestion, heartburn, and other symptoms of EC are noted. EC can be resectable or non-resectable. Allopathic drugs, including chemotherapy, combination therapy, immunotherapy, molecular-targeted therapy, and surgical procedures, can be used to treat resectable EC. They, however, are prone to side effects and consequences such as cachexia, tracheoesophageal fistula, anastomotic leakage, cardiopulmonary problems, and malnutrition, with malnutrition being more prevalent in EC. Hence, dietary management is crucial both during and after EC treatment. This includes dietary and nutritional changes during radiation/chemotherapy. More alkaloids, flavonoids, antioxidants, and other substances should be included in the diet. Foods that help prevent cancer growth such as broccoli, carrots, berries, etc. should be included in our everyday diet. This review highlights the importance of nutritional management for the treatment of EC.A healthy dietary condition improves patient outcomes and minimizes comorbidities. Nutritional management during and after EC treatment improves the person's immunity, increasing the likelihood of survival.

KEYWORDS: Esophageal cancer, Allopathic therapy(PD-1/PD-L1), Nutritional Management, Chemotherapy, Nutrients, diet

I. INTRODUCTION:

A condition known as cancer occurs when some body cells grow out of control and spread to other body regions. In the past decades, cancer has become one of the leading causes of morbidity and mortality worldwide. Female breast, lung, colorectal, and prostate cancers made up half of the total cancer burden in the highest HDI regions in 2008, whereas esophageal, stomach, and liver cancers were more prevalent in medium HDI regions and together these seven cancers made up 62% of the total cancer burden in medium to very high HDI areas. Cervical cancer was more prevalent than breast cancer and liver cancer in areas with poor HDI. [1] Being ranked ninth for cancer incidence and sixth for cancer deaths in 2013, esophageal cancer is one of the most lethal malignancies in the world. Esophageal cancer saw 442,000 new cases and 440,000 deaths in 2013. [2]

History-

Esophageal cancer was first described over 2,000 years ago in China. Galen defined "fleshy growths" as an esophageal blockage factoring in cachexia and having a lethal effect in the second century. Ibn Zuhr, also known as Avenzoar in the West (1091–1162), was the preeminent figure in Arabo-Islamic medicine in the 11th century. He described esophageal cancer symptoms as "beginning with mild pain and difficulty in swallowing" and recommended inserting a long silver cannula into the esophagus for pouring liquids. [3]

Description-

In terms of mortality and prognosis, esophageal carcinoma is a dangerous malignancy. Esophageal cancer prognosis is strongly influenced by local invasion as well as metastasis to nearby and distant bodily tissues. Esophageal cancer is notoriously aggressive and can spread through several different channels, including hematogenous metastasis, lymphatic dissemination, and direct extension.

The local spread of esophageal cancer is significantly influenced by the absence of serosa in

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 506-522 www.ijprajournal.com ISSN: 2249-7781

the esophageal wall. The thyroid gland, trachea, larynx, lung, pericardium, aorta, and diaphragm are among the nearby tissues of the neck and thorax that the primary tumor can quickly invade in the absence of an anatomical barrier. The esophagus has a large lymphatic drainage system. It is drained by two distinct lymphatic plexuses, one of which emerges from the mucosal layer and the other from the muscular layer.

All of the lymphatic channels of the esophagus connect, albeit the majority of the lymphatic fluid from the top two-thirds of the esophagus tends to flow upward and the lymph from the lower third of the esophagus flows substantially downward. Because of this, lymphatic fluid from any area of the esophagus has the potential to flow in both directions and reach the intrathoracic or intra-abdominal lymph nodes. Moreover, esophageal cancer can spread hematogenously to the liver, lungs, bones, kidney, adrenal glands, and brain, in decreasing order of frequency. [4]

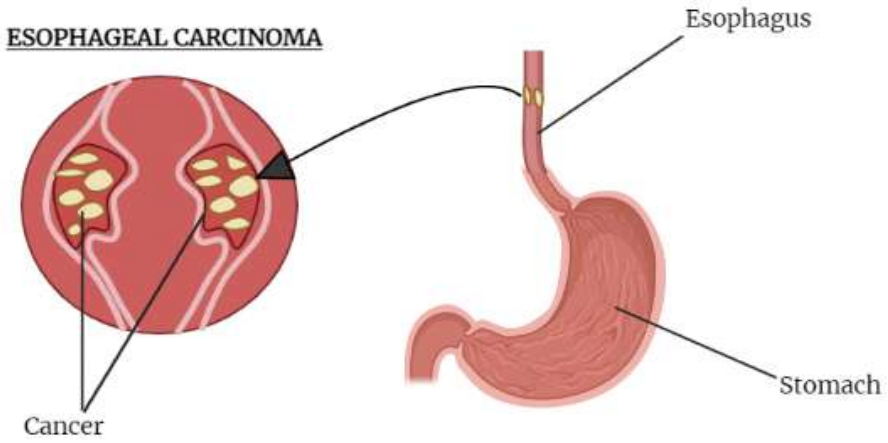

Fig. 1.1 Esophageal Cancer

Symptoms-

Dysphagia (dys = abnormal + phagia = swallowing) is nearly invariably the first sign of esophageal cancer. Early symptoms may include trouble swallowing solid foods, but if the esophageal obstruction worsens, issues with liquid swallowing may also develop. Due to the possibility that chronic gastroesophageal reflux disease (GERD) and adenocarcinoma of the esophagus are connected, GERD symptoms such as heartburn and indigestion may also be present. This is frequently reported as scorching pain in the upper abdomen, immediately below or below the breastbone.

Unexpected weight loss is a symptom of esophageal cancer that affects more than half of patients. Esophageal malignancies can bleed, resulting in blood vomiting or melena passage (black, tarry stools). The bleeding may occasionally be minute and invisible to the human eye. Decreased red blood cell count may induce weakness in the patient, and since blood loss is the likely cause, iron deficiency anemia is most likely the cause.

The upper abdomen or the lower chest may be painful due to esophageal cancer. There can be discomfort in the back or other areas nearby the chest if the cancer has advanced. Patients may feel hoarseness of voice as a result of vocal cord injury brought on by stomach acid refluxing into the throat. Hypersalivation and a sour taste in the back part of the tongue caused by reflux are both described as water brash.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 506-522 www.ijprajournal.com ISSN: 2249-7781

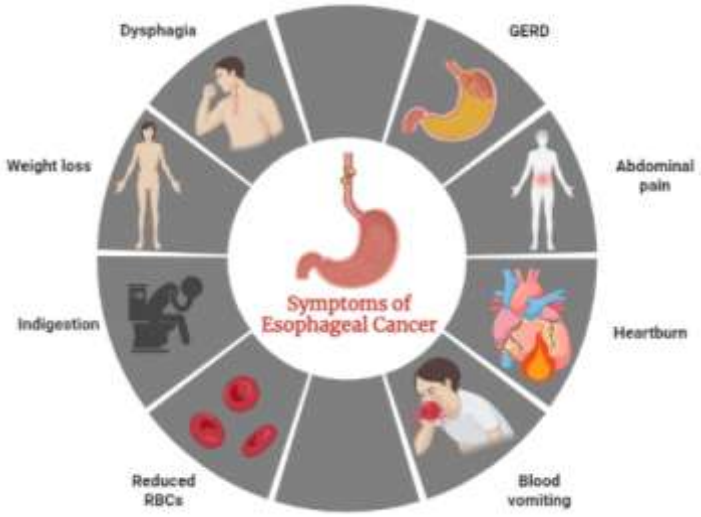

Fig. 1.2 Symptoms of Esophageal Cancer

Diagnosis-

By using endoscopy and biopsy, esophageal cancer is diagnosed. A gastroenterologist can do an endoscopy when swallowing issues (dysphagia) manifest. The gastroenterologist can obtain a tissue sample (biopsy) if a lump or tumor is observed in the esophagus.A pathologist uses a microscope to examine the tissue biopsy, and if cancer cells are discovered, the clinical diagnosis is then verified. Plain X-rays, CT scans, and PET scans may be employed to check for metastases and cancer spread to different body parts. [5]

While malignancies discovered through a BE monitoring program or as an incidental finding during a gastroscopy conducted for another reason may be at an early stage, most esophageal cancers are discovered after symptoms such as dysphagia have developed and tumors have spread locally. As a result, only one out of every eight esophageal tumors is detected at an early stage (T1). High-resolution white-light endoscopy reveals mucosal abnormalities during gastroscopy. If erosions, ulcers, strictures, or metaplasia are seen, the endoscopist must determine if the cause is nonneoplastic or neoplastic. Discolorations, finely granulated surfaces (orange peel look), and little elevations and troughs in the Barrett layer are all dysplastic indications. [6]

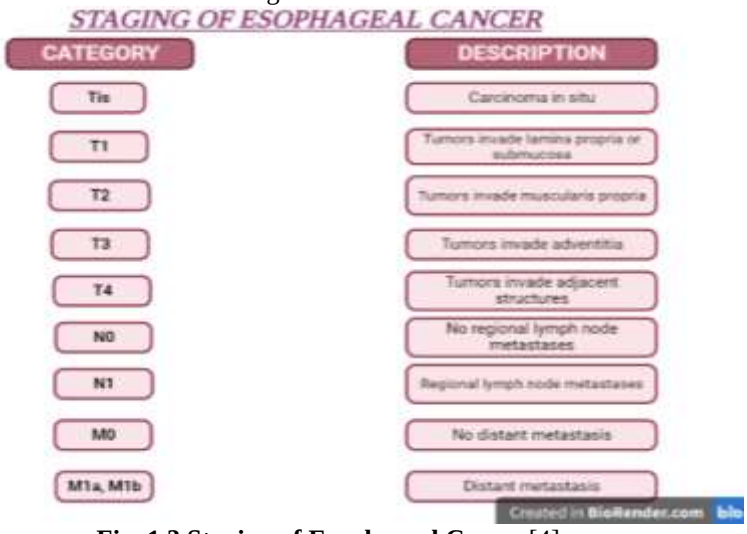

Fig. 1.3 Staging of Esophageal Cancer[4]

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 506-522 www.ijprajournal.com ISSN: 2249-7781

Types-

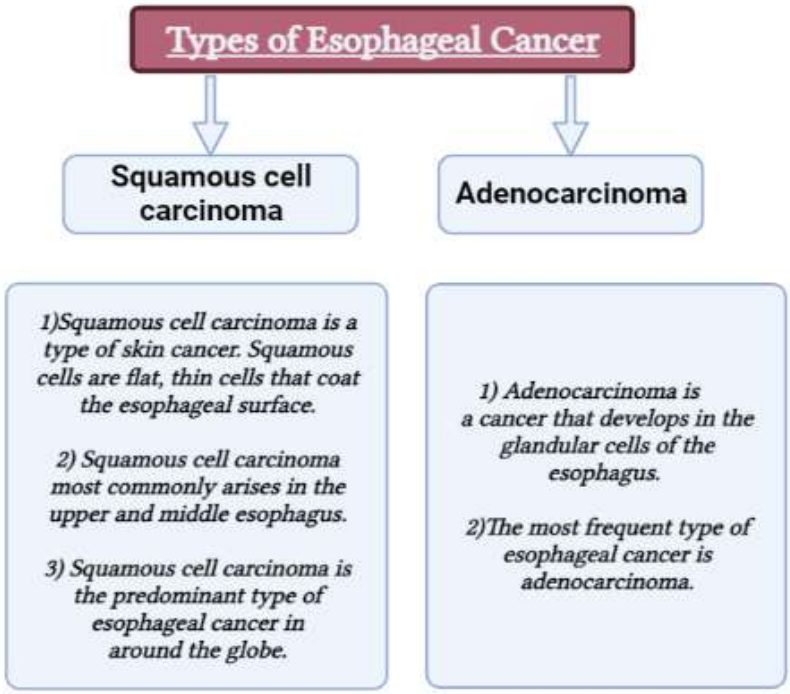

Fig. 1.4 Types of Esophageal Cancer

II. CAUSES AND RISK FACTORS:

There are several causes and risk factors of esophageal cancer and they are divided according to their types:

Squamous cell carcinoma-

1. **Gender and race**: In most nations, men are more likely than women to get esophageal squamous cell carcinoma; in the United States, black men are more likely to develop the disease than white men. [7]
2. **Smoking**: Compared to non-smokers, smokers have a 5-fold increased risk of contracting this disease. [7]
3. **Alcohol**: Drinkers have a 50% greater risk than non-drinkers. Alcohol-related ESCC risk is increased by a deficiency in the enzyme aldehyde dehydrogenase 2 (ALDH2), which is responsible for the so-called alcohol flushing reaction. [8]
4. **Tobacco**: The consumption of "areca nut chewers," widespread in places like Southeast Asia and India and frequently combined with tobacco, has been associated with the emergence of squamous cancer. [9].
5. **Diet and nutrients**: Depending on the size of the sip, consuming 65 °C coffee raised the intraesophageal temperature by 6–12 °C [10]. Pickled vegetables are home to fungi and yeasts that could release mycotoxins, N-nitrosamines, and Roussin red methyl ester, among other possibly cancerous substances. [11]
6. **Genetics**: The emergence of esophageal squamous carcinoma is unquestionably correlated with some disorders that have a hereditary foundation, such as Tylosis, an autosomal dominant illness. [7]

Esophageal adenocarcinoma-

1. **Gastroesophageal reflux disease and Barrett's esophagus**: 10% of individuals with GERD will eventually develop Barrett's esophagus. [12] When compared to people without GERD-related symptoms, patients with recurrent heartburn or regurgitation have a roughly 5-fold higher chance of developing esophageal cancer. [13]
2. **Age**: According to reports, those over 50 are at an increased risk of being diagnosed with

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 506-522 www.ijprajournal.com ISSN: 2249-7781

esophageal adenocarcinoma, but no evidence was found to suggest that the risk increases significantly after that age. [14]

3. **Gender**: Yet, the incidence rate of esophageal adenocarcinoma is 38 times higher in men than in women, which may indicate that men are more prone to get Barrett's esophagus as well as to have it proceed to cancer once they already have it. [15]
4. **Obesity**: Increased abdominal obesity and body mass index (BMI) are both linked to a higher chance of developing cancer. According to research, both males and females with a BMI more than 25 had an increased chance of developing esophageal adenocarcinoma (OR = 2.2; 95% CI, 1.8-2.7) [16]
5. **Genetic aspect**: There is a strong genetic association (rg = 1.0; SE = 0.37) between BE and esophageal cancer and predicted a statistically significant polygenic overlap between the two [one-sided P = 1 10(-6)]. These findings strongly imply that BE and esophageal cancer development are caused by similar genes. [17]

Fig. 2.1 Risk Factors of Esophageal Cancer

III. COMPLICATIONS:

1. **Anemia**: Anemia in histological subtypes of esophageal cancer has tended to concentrate on squamous cell carcinoma. [18] This is because tumors generate inflammation, which lowers the formation of red blood cells. Many chemotherapy treatments are myelosuppressive, reducing the bone marrow's rate of producing new blood cells.
2. **Weight loss**: Several factors contribute to weight loss in esophageal cancer, including systemic inflammation and decreased calorie intake as a result of mechanical blockage from large tumors.[19] Neoadjuvant therapy and surgery further compound the consequences of weight loss because severe weight loss during or after treatment is also linked to a worse chance of survival.[20]
3. **Dysphagia**: It is characterized by difficulty in swallowing. Even after the radiation treatment is over, the side effects of radiation, including scarring and fibrosis, might impair the capacity of the throat muscles to operate normally. Another side effect of radiation is the narrowing of the swallowing canal, or "stricture."
4. **Cachexia**: Cachexia is made worse in esophageal cancer patients by feeding problems caused by the stage and location of the tumors well as by the side effects of neoadjuvant therapy
5. **Tracheoesophageal fistula**: It is an improper connection (fistula) between the esophagus and the

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 506-522 www.ijprajournal.com ISSN: 2249-7781

trachea, and bronchi and occurs after surgery, radiotherapy, chemotherapy, andlaryngectomy.

Postoperative complications-

1. **Anastomotic Leakage**: Failure of the anastomosis to heal is the most severe complication after esophageal surgery.[21] The percentage of leakage still ranges from 10% to 21.2% despite improvements in surgical procedures and perioperative management, and the rate of leakage still ranges from 10% to 21.2%.
2. **Pulmonary complications**: Patients undergoing esophagectomy frequently develop pulmonary problems like pneumonia, atelectasis, and respiratory insufficiency, which are the leading causes of postoperative mortality.[22] A role is also likely to be played by bronchial innervation disruption, postoperative respiratory muscle dysfunction, and inadequate airway protection in cases of recurrent laryngeal nerve injury.
3. **Cardiac complications**: After esophagectomy, atrial fibrillation (AF) is a common consequence that can be explained by the esophagus' close closeness to the left atrium. Hypertension and coronary artery disease are the risk factor for it. [23]
4. **Chylothorax**: Chylothorax after esophagectomy is an unusual but potentially deadly complication, with a reported prevalence of 0.4-4%, in which the digestive system (chyle) accumulated the in the chest [24].
5. **Recurrent laryngeal nerve palsy**: Damage to the RLN during an esophagectomy occurs frequently during the cervical dissection or the thoracic paratracheal lymph node dissection.

IV. PATHOPHYSIOLOGY:

Squamous cell carcinoma-

SCC can arise in both the middle and lower esophagus. Alcohol usage and cigarette use are major risk factors. Although most studies have found that alcohol is the primary risk factor, smoking in conjunction with alcohol use may have a synergistic impact and enhance the relative risk. The mechanism by which smoke and alcohol together enhance the risk of esophageal cancer has been widely explored.

Alcohol can harm cellular DNA by decreasing metabolic activity within the cell, reducing detoxifying function while increasing oxidation Alcohol acts as a solvent, particularly for fat-soluble molecules. As a result, the dangerous carcinogens in tobacco can more easily permeate the esophageal epithelium.Tobacco contains carcinogens such as aromatic amines, nitrosamines, polycyclic aromatic hydrocarbons, aldehydes, and phenols.

Other carcinogens, such as nitrosamines found in salted vegetables and preserved fish, have also been linked to esophageal cancer. The pathophysiology appears to be linked to squamous epithelial inflammation, which results in dysplasia and in situ malignant transformation.

Adenocarcinoma-

Adenocarcinoma of the esophagus occurs in around three-fourths of cases and has a clear relationship to gastroesophageal reflux syndrome (GERD). Untreated GERD can advance to Barrett's esophagus (BE), a condition in which the esophageal stratified squamous epithelium is replaced by a columnar epithelium. Chronic reflux of stomach acid and bile at the gastroesophageal junction, with subsequent esophageal injury, has been linked to the etiology of Barrett metaplasia.

Barrett esophagus becomes more common with age and is uncommon in children. Some studies have suggested that the degree of esophageal metaplasia may influence the risk of esophageal adenocarcinoma. The longer the damaged esophageal tract, the greater the chance of adenocarcinoma. Yet, because short-segment esophageal metaplasia is more common in the general population, many occurrences of adenocarcinoma occur in patients with this condition.

Obesity is another risk factor for EAC, particularly in people with predominantly abdominal fat distribution. By the production of adipokines and cytokines, hypertrophied adipocytes and inflammatory cells within fat deposits produce an environment of low-grade inflammation and promote tumor development. Adipocytes in the tumor microenvironment produce energy and aid in tumor development and progression. [25]

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 506-522 www.ijprajournal.com ISSN: 2249-7781

V. ALLOPATHIC REMEDIES:

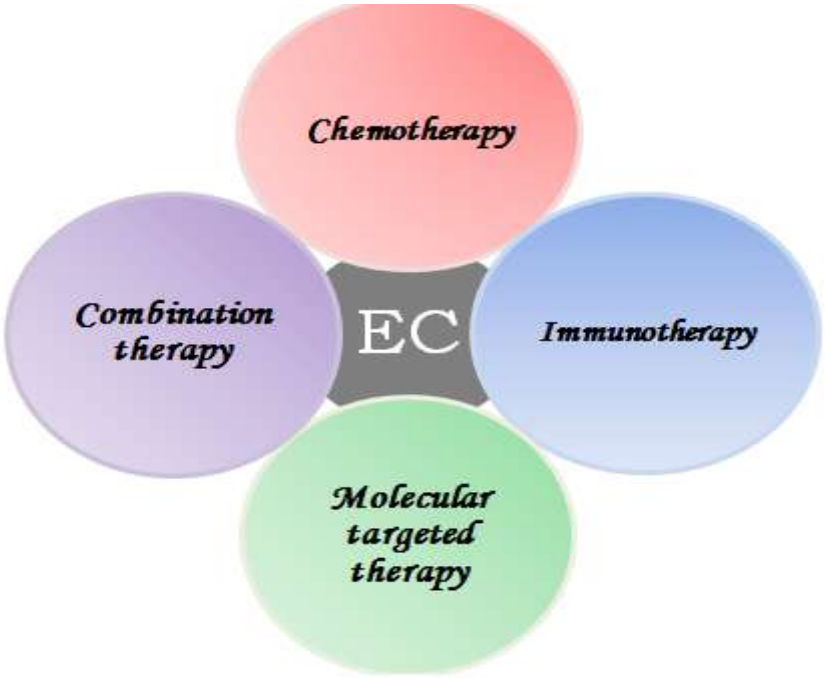

Fig. 3.1 Different Treatment Types in Allopathy for EC[26]

Immunotherapy-

Immunotherapy, the method of increasing the efficacy and specificity of immune cells to decrease cancer growth, is a hot study topic in cancer therapy, in addition to targeting intrinsic signaling in cancer cells. Cellular immunity can be broken down into multiple phases. To begin, the receptor on the surface of the T lymphocyte membrane selectively binds to the MHC on the surface of the antigen-presenting cell (APC). The combination of T cells and MHC will then cause further activation, proliferation, and differentiation. Ultimately, activated T cells will produce immunological responses. This network of signaling channels is critical in the progression of tumor immunity.

I] PD-1/PD-L1-targeted therapy:

The programmed cell death protein 1 (PD-1) pathway is thought to be an essential inhibitory mechanism in T cell failure. One PD-1 ligand, programmed cell death-ligand 1 (PD-L1), has been demonstrated to be expressed in a range of cancer cells, confirming that cancer cells can avoid the immune system's deadly effect.

As a result, PD-L1 inhibitors are regarded as excellently targeted medications for combating cancer cell evasion of T cells. Conventional PD-L1 inhibitors, such as pembrolizumab, can bind to PD-L1 on tumor cells, preventing PD-L1 from binding to PD-1 on T cells and therefore terminating T cell suppression, allowing T cells to attack cancer cells.

II] CTLA4 - targeted therapy:

CTLA4 (cytotoxic T-lymphocyte associated protein 4 is a negative regulator of T cell expression whose overexpression can reduce interleukin-2 expression (IL-2). CTLA4 can stop T cells in the G1 phase of the cell cycle, reducing particular immune activity and promoting cancer cell immune evasion. Some research has shown that CTLA4 can be used as an immune-based target for cancer treatment. Ipilimumab and tremelimumab are currently available CTLA4 inhibitors. Ipilimumab is a monoclonal antibody that can efficiently block CTLA4 and has been used successfully in the treatment of melanoma.

III] TIGIT-targeted therapy:

T cell Ig and ITIM domain (TIGIT) is an immunoglobulin from the Ig superfamily. Its expression can impair NK cell immunological responses, allowing tumor cells to elude their effects and lead to immune escape. As a result, TIGIT is an essential and worthwhile target for EC immunotherapy, with TIGIT inhibition as a possible immunotherapy method. Anti-TIGIT antibodies can be created to diminish TIGIT's

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 506-522 www.ijprajournal.com ISSN: 2249-7781

inhibitory effect on NK cells. Several anti-TIGIT antibodies, including tiragolumab and mAb-7, have recently been examined in clinical trials. [26]

Molecular- Targeted therapy-

Table. 1.1Molecular-Targeted Therapy[26,27]

Sr. No.	Treatment regimen	Cancer type	Clinical Phase	Drug Type	Mechanism
EGFR Pathway					
1)	Cetuximab	EC	II	Monoclonal antibody	EGFR is particularly targeted to prevent its activation, which slows tumor progression.
2)	Nimotuzumab	ESCC	-	Fully recombinant, humanized monoclonal antibody	-
3)	Gefitinib	EC		EGFR inhibitor	Potentially reduces cancer formation and progression by blocking EGFR downstream signaling in cells
4)	Icotinib	EC	II	Highly selective EGFR inhibitor	With strong EGFR expression, it is useful in the treatment of EC.
HER-2 Pathway					
5)	Trastuzumab	EAC	I/II	Humanized antibody against HER-2, a novel enzyme-cleavable linker, and a topoisomerase I inhibitor	Trastuzumab has the potential to slow the growth of malignancies that express HER-2.
6)	Lapatinib	EC, Breast cancer	III	Inhibitor of EGFR and HER-2	Apoptosis is significantly increased by inhibiting EGFR and HER2 phosphorylation and inactivating the MAPK and AKT signaling pathways.
VEGF/VEGFR Pathway					
7)	Bevacizumab	EAC	II/III	Monoclonal antibody	By blocking VEGF-A from attaching to VEGFR2, it can enhance vascular permeability and suppress tumor growth.
8)	Ramucirumab	EC	II	A new type of human	VEGFR2 is

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 506-522 www.ijprajournal.com ISSN: 2249-7781

				immunoglobulin G (IgG) 1 monoclonal antibody	particularly inhibited and its interaction with ligands is blocked, reducing angiogenesis, and triggering tumor cell death.
9)	Apatinib	ESCC	II	Small-molecule inhibitor	Suppresses the activity of VEGFR and HER2
HGF/ c- MET Pathway					
10)	Rilotumumab	EC	III	Humanized monoclonal antibody	HGF is targeted to block its interaction with c-Met.

(EC- Esophageal Cancer, ESCC- Esophageal Squamous Cell Carcinoma, EAC- Esophageal Adenocarcinoma)

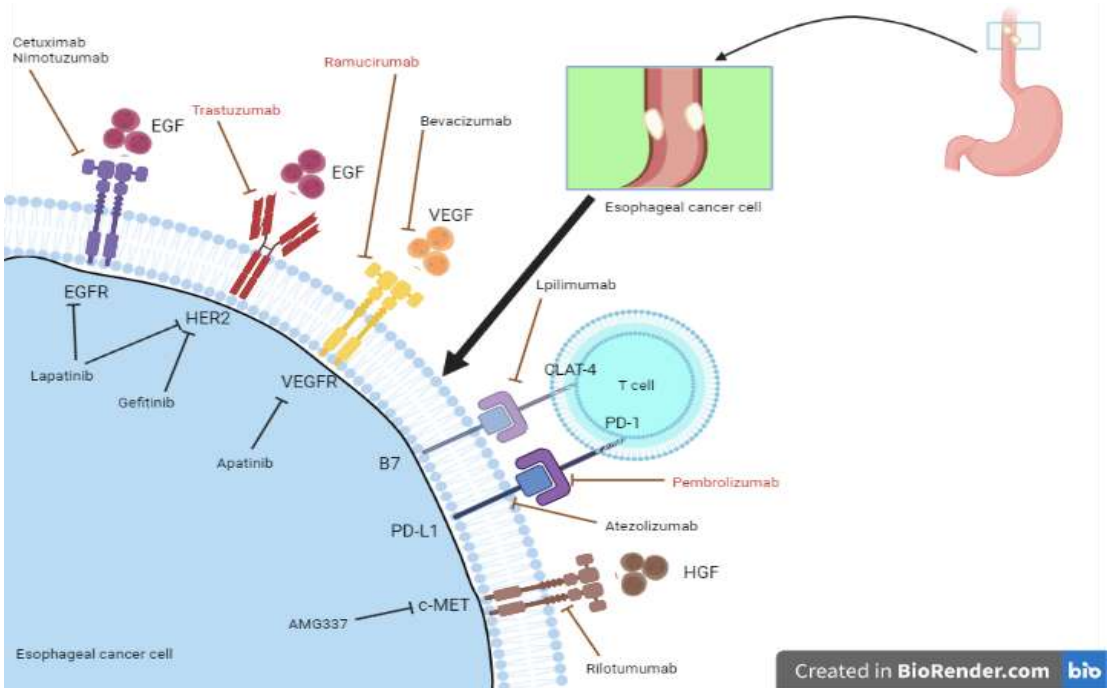

Fig. 3.2Molecular–Targeted Therapy [26]

Chemotherapy-

Dox is a commonly used anticancer medication that generates reactive oxygen species (ROS), which cause DNA damage and degrade the double-layer membrane structure. Several delivery techniques have been developed to improve the efficacy of Dox in EC treatment. Due to prolonged circulation time and improved permeability and retention, Dox is successfully administered to the tumor site and demonstrates a strong inhibitory effect on tumor growth in esophageal xenograft cancer models.

Another treatment for advanced EC is paclitaxel-based radiochemotherapy. Heavy carbon ion beam irradiation combined with docetaxel has a synergistic effect on EC, making it a promising therapy option for locally progressed ESCC. Docetaxel toxicity and drug resistance limit its widespread clinical use; resistance is related to the upregulation of the P-gp efflux pump and resistance to apoptosis.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 506-522 www.ijprajournal.com ISSN: 2249-7781

Another potential anticancer medication is camptothecin. During the therapy of ESCC, gimatecan, a novel type of oral camptothecin, inhibits topoisomerase I expression and bioactivity, causes DNA damage and S-phase arrest, and induces apoptosis. [27]

Combination therapy-

Table. 1.2Combination Therapy (Mechanism Based) [27]

Sr. No.	Treatment regimen	Cancer Type	Mechanism
CISPLATIN-BASED COMBINATION THERAPY			
1)	Apple pomace (AP) water extract, cisplatin, and 5-fluorouracil (5-FU)	ESCC	AP water extract decreases chemotherapy treatment side effects and suppresses metastasis-related factors such as MMP2, MMP9, TM4SF3, and CXCR4.
2)	VE-822 and cisplatin	ESCC	VE-822 increases tumor cell susceptibility to cisplatin in ESCC cells, particularly those with the ataxia-telangiectasia mutation.
3)	Tiplaxtinin and cisplatin	ESCC	Tiplaxtinin and cisplatin together enhance apoptosis, increase the buildup of reactive oxygen species, and inhibit tumor growth.
5- FU- BASED COMBINATION THERAPY			
4)	CA3 and 5-FU	EAC	CA3 suppresses the transcription of YAP/TEAD. Combined therapy lowers YAP1, SOX9, and Ki67 expression in mouse models.
5)	Hesperetin and 5-FU	ESCC	Combination therapy successfully causes cell death, decreases BCL-2 expression, and increases BAX, cleaved caspase-3, and cleaved caspase-9 expression.
6)	Puerarin and 5-FU	ESCC	When used together, they greatly reduce cell proliferation and induce apoptosis.

Table. 1.3Combination Therapy (Clinical Trial Based) [20]

Sr. No.	Treatment regimen	Cancer Type	Clinical Trials
CISPLATIN + RADIATION THERAPY			
1)	Pemetrexed, cisplatin, and radiation therapy	Esophageal or gastroesophageal junction cancer	I
2)	PPX with cisplatin, and radiation therapy	EC	II
CISPLATIN + RADIATION THERAPY + SURGERY			
3)	Irinotecan, cisplatin, radiation	EC	II/III

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 506-522 www.ijprajournal.com ISSN: 2249-7781

	therapy, and surgery		
4)	Cisplatin, 5-FU, radiation therapy, and surgery	EC	III
CISPLATIN + ANTIBODY			
5)	5-FU/cisplatin, radiation therapy plus cetuximab	EC	II
6)	Docetaxel, cisplatin, 5-FU, bevacizumab, leucovorin	EC, Stomach cancer	II
CISPLATIN + OTHER DRUGS			
7)	G17DT immunogen, cisplatin, 5-FU	EC, Gastric cancer	III
8)	Paclitaxel and cisplatin	ESCC	II

VI. NUTRITIONAL MANAGEMENT:

Malnutrition and poor dietary intake are frequently connected with esophageal cancer. The nutritional care of these patients may vary depending on the type of therapy and stage of disease, to alleviate symptoms, improve nutritional status, and improve quality of life. Additionally, cancer cachexia affects a large proportion of esophageal cancer patients, making it a crucial concern that the multidisciplinary team must address. Due to a lack of consistent evidence for patients undergoing esophagectomy, the optimal form of feeding (i.e., enteral/parenteral nutrition (EN/PN), immunonutrition, oral supplements, etc.), as well as the right time of feeding, is source of contention in postoperative care. Long-term dietary demands are especially critical for patients with both resectable and incurable diseases, given that the majority of these patients strive to achieve their caloric and protein requirements.

Severe weight loss is caused in part by the illness process and is frequently exacerbated by chemotherapy/radiotherapy treatment. Malnutrition affects 60-85% of individuals with esophageal cancer. Chemotherapy and radiotherapy both have an impact on the nutritional status by causing weight loss and muscle wastage. [28] When cancer patients get radiotherapy or pharmaceuticals, their systems develop resistance to specific agents designed to target cancer cells, inhibiting effective cancer treatments. Natural compounds, such as alkaloids and terpenes, prevent EC cell resistance. [29]

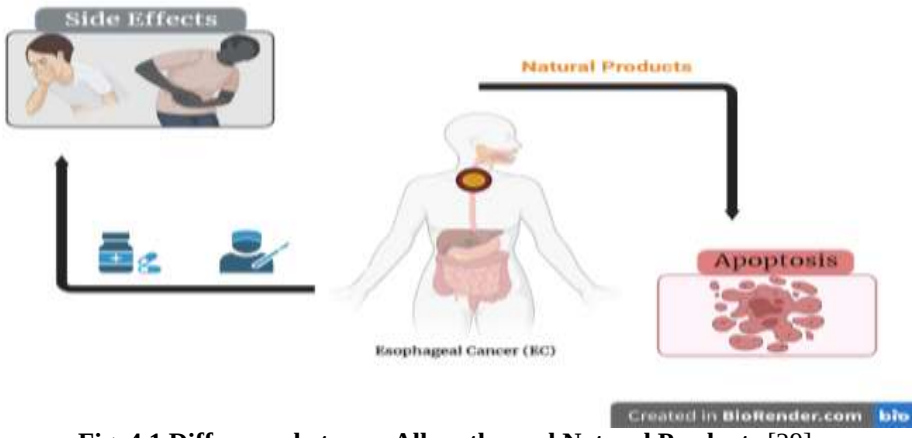

Fig. 4.1 Difference between Allopathy and Natural Products [29]

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 506-522 www.ijprajournal.com ISSN: 2249-7781

Natural substances ranging from alkaloid to triterpene, extracts, and decoction (water obtained from crude medicines) exhibit apoptotic effects on esophageal squamous cell carcinoma. Hadisaputri et al. reported that Curcumazedoaria (CZ) rhizome extract has anti-angiogenic, anti-metastatic, and apoptotic effects on esophageal carcinoma cells. In TE-8 and HET-1A cells, CZ extract activated cleaved caspase-9, -3, cleaved PARP, and PTEN while deactivating Bcl-2, MMP-2, and AKT, respectively FGFR1, and STAT3. CZ extract was shown to contain appropriate ingredients that modify multi-targets against proteins in esophageal carcinoma cells when subcutaneously injected into BALB/c mice. [29]

Citrus fruits, which include oranges, mandarins, limes, lemons, grapefruits, and citrons, are members of the Rutaceae family. Citrus fruits help to prevent cancer because they are high in vitamin C and other antioxidants, antimutagenic, and antiproliferative components. Experiments have shown that vitamin C destroys cancer cells, slows tumor growth, and is cytotoxic to cancer, suggesting that it may lessen the incidence of stomach cancer. Citrus fruits are high in vitamin C and secondary metabolites such as flavonoids, alkaloids, coumarins, limonoids, carotenoids, phenol acids, and essential oils, which protect against cancer. By preventing oxidation, shielding DNA from damage, and triggering apoptosis in cancer cells, these components have antioxidant, antimutagenic, and antiproliferative properties. Citrus fruit's anticancer effects were obtained from an inhibitory effect on epithelial-to-mesenchymal transition and interfering with the classical transforming growth factor-1-drosophila moms versus the decapentaplegic protein-Snail/Slug axis, according to a recent study. [30]

Nutritional Management in general: -

1) **Meat-**

- **Red meat**: In numerous types of research, red meat has been linked to an increased risk of EC. High-temperature cooking methods and the heme iron found in red meat are likely to contribute to the risk. The latter promotes endogenous N-nitroso compound production. White meat has a considerably decreased risk of esophageal cancer, most likely due to its lower heme iron level. A higher red-meat-to-poultry ratio has been linked to an increased risk of SCC.
- **Processed meat**: Consumption of processed meat is most likely related to overall EC risk. They are rich in N-Nitroso compounds, cooking of which also leads to the generation of heterocyclic amines (HCA) and polycyclic aromatic hydrocarbons (PAH). This increases the potential for mutagenesis. Mutagenic HCAs and PAHs produced by cooking meats at high temperatures, such as pan frying or grilling over an open flame, have been proposed to contribute to EC risk. [31,32]
- **Fish**:Fish-eating as a risk factor in esophageal carcinogenesis has received little attention. According to research, it plays little or no direct impact on risk reduction. Yet, including fish and other lean meats may imply less consumption of red and preserved meats, resulting in a perceived protective effect. [32]

2) **Plant-Based Products-**

- **Fruit and vegetables:**The consumption of fruits and vegetables has been linked to a lower incidence of esophageal cancer. Fiber, lutein, and folate are thought to mediate the beneficial benefits. The link appears to be more pronounced in adenocarcinomas than in squamous cell carcinomas. Several studies have found that a diet high in fruits and vegetables is related to a considerable reduction in SCC. [33]
- **Dietary fiber:**Dietary fiber has anticarcinogenic properties and may protect against esophageal cancer. Dietary fiber is suggested to help with weight control and decrease carcinogenesis via controlling gastric reflux. [34]
- **Tea:**Teas are assumed to have a protective impact since their constituents frequently exhibit antioxidative, anti-inflammatory, antibacterial, and immunostimulant activities in vitro. Tea consumption may prevent N-nitroso-compound-induced esophageal carcinogenesis. [35]
- **Coffee**:Coffee has a variety of anticarcinogenic compounds. Caffeine inhibits cell proliferation produced by cyclin-dependent kinase-4. Cafestol and kahweol, two more components, may help to prevent DNA damage. Maté is a tea-like infusion prepared from the leaves of a perennial tree native to South America. A meta-analysis indicated an increased risk of cancer with maté. Green tea

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 506-522 www.ijprajournal.com ISSN: 2249-7781

and coffee consumption have been shown to protect against EC; however, black tea consumption has no connection with any type of EC. [35,36]

3) **Micro and Macro- Nutrients-**

- **Folate:** Folate is a water-soluble B vitamin found in leafy green vegetables, lentils, and citrus fruits. It is strongly linked to a lower risk of EC. Folate deficiency has been linked to cancer development through its effects on DNA synthesis, repair, and methylation. Other B vitamins are required for efficient folate metabolism, which is hampered by smoking and alcohol usage. [37]
- **N- nitroso compounds:** N-nitroso compounds are thought to behave as pro-oxidants, catalyzing lipid peroxidation and causing DNA damage in tissues. N-nitroso compounds can be found in processed foods and the metabolism of heme iron. [38]
- **Dietary fat intake:** Dietary fat intake has been linked to an increased risk of EC, while the evidence is mixed. One prospective investigation discovered no link between dietary fat intake and EC. However, the study discovered a protective impact of polyunsaturated fat consumption in participants with a normal BMI in AC. Another study found that diets high in dairy fat were linked to a higher meat-and-fat pattern, which raised the risk of AC. [39]
- **Carbohydrates:** Carbohydrates have been researched in terms of their glycemic load (GL) and glycemic index (GI), and they may have a beneficial relationship with EC and SCC in particular. It is hypothesized that high GI meals contain readily absorbable carbs, resulting in high blood glucose levels and, as a result, increased insulin demand. This unintentionally boosted Insulin-Like Growth Factor 1 (IGF1), which has been linked to the progression of numerous malignancies. [40]

Nutritional Management During Treatment: -

1) **Radiation-**

Radiation therapy frequently causes esophagitis, early satiety, reflux, and esophageal stricture in patients with esophageal cancer. To avoid additional nutritional depletion, dietary intervention should begin as soon as symptoms appear. There are guidelines for managing dysphagia and avoiding potential irritants (for example, acidic foods, caffeine-containing goods, and difficult-to-chew foods). A high-protein, moderate-fat diet consumed in small, frequent meals can help increase diet tolerance. Supplements high in calories and protein are frequently required for nutritional replacement and can be administered orally or via a bypass feeding tube.

2) **Chemotherapy-**

Nausea, vomiting, stomatitis, and diarrhea are all possible side effects depending on the type of chemotherapy and the protocol used in patients with esophageal cancer. Adjustments in dietary recommendations should be consistent with the problem affecting the patient's nutritional status. Although dietary management rarely eliminates the problems, manipulation of the patient's oral intake often can successfully reduce the severity of symptoms. Nutritional strategies are often combined with drug therapy for improved results.

3) **Vagotomy-**

When esophageal resection is combined with a vagotomy, patients may experience stomach stasis, early satiety, distention, nausea/vomiting, and trouble eating enough to meet daily nutrient demands. Since fat-containing foods may further prolong gastric emptying, short, frequent meals of low-fat foods should be chosen first. To establish which foods are best accepted by each individual, some experimentation with meal selections and responses to foods is required.

4) **Colonic or Jejunal Interposition-**

When there is inadequate tissue for reanastomosis, interposition may be undertaken. The colonic or jejunal portion, on the other hand, lacks regular peristaltic action and relies on gravity for food passage. As a result, the patient may continue to experience dysphagia and irritation with the delayed swallowing process. Nutritional advice includes suggestions for eating semisolid foods and drinking liquids after each bite to cut down on meal preparation time.

5) **Esophageal Dilation and Prosthesis-**

A prosthesis or stent may be used to treat dysphagia in advanced stages of esophageal cancer. Dilation of the esophagus to more than 13 mm, followed by implantation of a prosthetic tube, facilitates luminal patency and food transit. Food modification entails avoiding foods that may clog the esophagus or adhere to the prosthesis's sides. Although this is a palliative treatment, it can enhance food intake for four to six months

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 506-522 www.ijprajournal.com ISSN: 2249-7781

following installation. When dilatation is performed without stent implantation, whether for food passage or merely to handle oral secretions, the improvement of dysphagia often lasts only a few days or weeks. In such circumstances, nutritional support using a PEG tube or a pre-existing feeding jejunostomy tube can give the most effective nutrition maintenance. [41]

A Diet Recommended by Memorial Sloan Kettering (MSK) Cancer Centre: -

Table. 2.1Diet Plan by MSK Cancer Centre

Sr. No.	Food Group	Food	Calories	Proteins (grams)
1)	Meat, beans, and eggs	1 cup cooked dried beans	240	4
		½ cup chicken salad	200	14
		3 ounces tuna canned in oil	170	25
		¼ cup egg substitute	25	5
2)	Nuts and seeds	1-ounce brazil nuts (6 to 8 nuts)	190	4
		1-ounce walnuts (14 halves)	185	4
		1 ounce shelled sunflower seeds	175	6
		1 ounce of almonds (about 24)	165	4
3)	Dairy	6 ounces of sweetened yogurt	130	5
		½ cup creamed cottage cheese	115	7
		¼ cup (1 ounce) shredded cheese	100	22
		1 tablespoon peanut butter	95	4
4)	Fats	2 tablespoons sour cream	50	1
		1 tablespoon butter, margarine, oil, or mayonnaise	100	0
		2 tablespoons gravy	40	1
5)	Sweets	1 tablespoon honey	60	0
		1 tablespoon sugar, jam, jelly, or chocolate syrup	50	0
6)	Meal replacements	1 meal replacement bar	200	15
		1 scoop (1 ounce) protein powder	100	15
		1 tablespoon protein powder	40	5

Nutritional Management for Prevention of Cancer: -

Obesity, nutrient-depleted meals such as concentrated sweets and refined flour products, which contribute to impaired glucose metabolism (which leads to diabetes), poor fiber intake, red meat consumption, and an imbalance of omega 3 and omega 6 fats all contribute to an increased risk of cancer. Consumption of flax seed, particularly its lignan fraction, as well as enough fruits and vegetables like carrots, berries, cinnamon, nuts, etc., will reduce cancer risk. Allium and cruciferous veggies are particularly helpful, with broccoli sprouts containing the highest concentration of sulforaphane. Selenium, folic acid, vitamin B-12, vitamin D, chlorophyll, and antioxidants such as carotenoids (α-carotene, β-carotene, lycopene, lutein, and cryptoxanthin) are all protective ingredients in a cancer prevention diet. [42] Smokeless tobacco products, such as dipping and chewing tobacco, can also cause cancer, especially esophageal, mouth and throat, and pancreatic

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 506-522 www.ijprajournal.com ISSN: 2249-7781

cancer. The amount of alcohol consumed raises the risk of acquiring cancer.

VII. CONCLUSION:

Esophageal cancer is the world's tenth most prevalent cancer. According to Globocan 2020, the global number of new cancer cases is predicted to reach 19.3 million, with 10 million fatalities. When it came to EC, there were 604,100 new cases and 544,076 fatalities, accounting for 3.1% and 5.5% of all newly diagnosed cancer cases and deaths, respectively. Furthermore, the prevalence of esophageal squamous cell carcinoma (ESCC) in Asia is statistically expected to be the highest in the last 5 years, with 2020 as the benchmark. As per the review, red meat, spicy foods, hot beverages, and dietary changes that include a low fiber intake, and an imbalance in omega 3 and omega 6 fats, among other things, are responsible for the development of EC. The common therapies used for treating EC have been associated with several side effects, of which malnutrition is the most prevalent. When compared to patients with other digestive and extra-digestive neoplasia, esophageal cancer had the highest incidence (78.9%). Thus, nutritional support has been found to help in the treatment of EC, thereby increasing the survival rate. Existing treatments for preventing esophageal cancer mostly involve increased consumption of vitamin C, antioxidants, anthocyanidins, and dietary fiber. Citrus fruit consumption lowered the risk of total ESCC as well as ESCC and EAC combined. As a result, natural products are promising in terms of treating esophageal cancer. This is critical for maximizing patients' chances of complete and speedy recovery from esophageal surgery.

REFERENCES:

[1]. Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008–2030): a population-based study. The lancet oncology. 2012 ;13(8):790-801.

[2]. Schizas D, Lidoriki I, Moris D, Liakakos T. Nutritional management of esophageal cancer patients. Esophageal Abnormalities. 2017.

[3]. Lerut T, Wiesel O. History of esophagectomy for cancer of the esophagus and the gastroesophageal junction. Annals of translational medicine. 2021;9(10).

[4]. Napier KJ, Scheerer M, Misra S. Esophageal cancer: A Review of epidemiology, pathogenesis, staging workup and treatment modalities. World journal of gastrointestinal oncology. 2014;6(5):112.

[5]. Abbas G, Krasna M. Overview of esophageal cancer. Annals of cardiothoracic surgery. 2017;6(2):131.

[6]. Meves V, Behrens A, Pohl J. Diagnostics, and early diagnosis of esophageal cancer. Visceral Medicine. 2015;31(5):315-8.

[7]. Wheeler J.B., Reed C.E., "Epidemiology of esophageal cancer", Surgical Clinics, 2012; 92(5): 1077-1087.

[8]. Brooks PJ, Enoch MA, Goldman D, Li TK, Yokoyama A. The alcohol flushing response: an unrecognized risk factor for esophageal cancer from alcohol consumption. PLoS medicine. 2009;6(3): e1000050.

[9]. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Betel-quid and areca-nut chewing and some areca-nut-derived nitrosamines. IARC monographs on the evaluation of carcinogenic risks to humans. 2004; 85:1.

[10]. De Jong UW, Day NE, Mounier-Kuhn PL, Haguenauer JP. The relationship between the ingestion of hot coffee and intraoesophageal temperature. Gut. 1972;13(1):24.

[11]. Wen-Xin Z, Meng-Shan X, Guang-Hui W, Ming-Yao W. Quantitative analysis of Roussin red methyl ester in pickled vegetables. Cancer research. 1983;43(1):339-41.

[12]. Fennerty MB. Barrett's-related esophageal cancer: has the final hurdle been cleared, now paving the way for human chemoprevention trials? Gastroenterology. 2002;122(4):1172-5.

[13]. Cook MB, Corley DA, Murray LJ, Liao LM, Kamangar F, Ye W, Gammon MD, Risch HA, Casson AG, Freedman ND, Chow WH. Gastroesophageal reflux in relation to adenocarcinomas of the esophagus: a pooled analysis from the Barrett's and Esophageal Adenocarcinoma Consortium (BEACON). PloS one. 2014;9(7): e103508.

[14]. Bhat S, Coleman HG, Yousef F, Johnston BT, McManus DT, Gavin AT, Murray LJ. Risk of malignant progression in Barrett's esophagus patients: results from a large

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 506-522 www.ijprajournal.com ISSN: 2249-7781

population-based study. Journal of the National Cancer Institute. 2011;103(13):1049-57.

[15]. Kubo A, Corley DA. Marked regional variation in adenocarcinomas of the esophagus and the gastric cardia in the United States. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2002;95(10):2096-102.

[16]. Corley DA, Kubo A, Zhao W. Abdominal obesity, and the risk of esophageal and gastric cardia carcinomas. Cancer Epidemiology Biomarkers & Prevention. 2008;17(2):352-8.

[17]. Ek W.E., Levine D.M., D'Amato M., Pedersen N.L., Magnusson P.K., Bresso F., Onstad L.E., Schmidt P.T., Törnblom H., Nordenstedt H., and Romero Y., Germline genetic contributions to risk for esophageal adenocarcinoma, Barrett's esophagus, and gastroesophageal reflux, Journal of the National Cancer Institute, 2013;105(22):1711-1718.

[18]. Zenda S, Hironaka S, Boku N, Yamazaki K, Yasui H, Fukutomi A, Yoshino T, Onozawa Y, Nishimura T. Impact of hemoglobin level on survival in definitive chemoradiotherapy for T4/M1 lymph node esophageal cancer. Diseases of the Esophagus. 2008;21(3):195-200.

[19]. Deans DA, Tan BH, Wigmore SJ, Ross JA, De Beaux AC, Paterson-Brown S, Fearon KC. The influence of systemic inflammation, dietary intake, and stage of disease on rate of weight loss in patients with gastro-oesophageal cancer. British journal of cancer. 2009;100(1):63-9.

[20]. Adenis A, Tresch E, Dewas S, Romano O, Messager M, Amela E, Clisant S, Kramar A, Mariette C, Mirabel X. Clinical complete responders to definite chemoradiation or radiation therapy for oesophageal cancer: predictors of outcome. BMC cancer. 2013; 13:1-8.

[21]. Low DE, Kuppusamy MK, Alderson D, Cecconello I, Chang AC, Darling G, Davies A, D'Journo XB, Gisbertz SS, Griffin SM, Hardwick R. Benchmarking complications associated with esophagectomy. Annals of surgery. 2019;269(2):291-8.

[22]. Whooley BP, Law S, Murthy SC, Alexandrou A, Wong J. Analysis of reduced death and complication rates after esophageal resection. Annals of surgery. 2001;233(3):338.

[23]. Hummel R, Bausch D. Anastomotic leakage after upper gastrointestinal surgery: surgical treatment. Visceral medicine. 2017;33(3):207-11.

[24]. Lagarde SM, Omloo JM, de Jong K, Busch OR, Obertop H, van Lanschot JJ. Incidence and management of chyle leakage after esophagectomy. The Annals of thoracic surgery. 2005 ;80(2):449-54.

[25]. Napier KJ, Scheerer M, Misra S. Esophageal cancer: A Review of epidemiology, pathogenesis, staging workup and treatment modalities. World journal of gastrointestinal oncology. 2014;6(5):112. Yang L, Shi P, Zhao G, Xu J, Peng W, Zhang J, Zhang G, Wang X, Dong Z, Chen F, Cui H. Targeting cancer stem cell pathways for cancer therapy. Signal transduction and targeted therapy. 2020 ;5(1):8.

[26]. Yang L, Shi P, Zhao G, Xu J, Peng W, Zhang J, Zhang G, Wang X, Dong Z, Chen F, Cui H. Targeting cancer stem cell pathways for cancer therapy. Signal transduction and targeted therapy. 2020 ;5(1):8.

[27]. He S., Xu J., Liu X. and Zhen Y., Advances, and challenges in the treatment of esophageal cancer. Acta Pharmaceutica Sinica B, 2021;11(11):3379-3392.

[28]. Schizas D, Lidoriki I, Moris D, Liakakos T. Nutritional management of esophageal cancer patients. Esophageal Abnormalities. 2017.

[29]. An J., An S., Choi M., Jung J.H. and Kim B., Natural Products for Esophageal Cancer Therapy: From Traditional Medicine to Modern Drug Discovery. International Journal of Molecular Sciences, 2022; 23(21): 13558.

[30]. Zhao W., Liu L. and Xu S. Intakes of citrus fruit and risk of esophageal cancer: A meta-analysis. Medicine, 2018; 97(13).Choi Y., Song S., Song Y., and Lee J.E., Consumption of red and processed meat and esophageal cancer risk: meta-analysis. World journal of gastroenterology: WJG, 2013; 19(7): 1020.

[31]. Choi Y., Song S., Song Y., and Lee J.E., Consumption of red and processed meat and esophageal cancer risk: meta-analysis.

World journal of gastroenterology: WJG, 2013; 19(7): 1020.

[32]. Salehi M., Moradi-Lakeh M., Salehi M.H., Nojomi M. and Kolahdooz F., Meat, fish, and esophageal cancer risk: a systematic review and dose-response meta-analysis. Nutrition reviews, 2013; 71(5): 257-267.

[33]. Liu J., Wang J., Leng Y. and Lv, C., Intake of fruit and vegetables and risk of esophageal squamous cell carcinoma: a meta-analysis of observational studies. International journal of cancer, 2013; 133(2): 473-485.

[34]. Coleman H.G., Murray L.J., Hicks B., Bhat S.K., Kubo A., Corley D.A., Cardwell C.R. and Cantwell M.M., Dietary fiber and the risk of precancerous lesions and cancer of the esophagus: a systematic review and meta-analysis. Nutrition reviews, 2013; 71(7): 474-482.

[35]. Zheng J.S., Yang J., Fu Y.Q., Huang T., Huang Y.J., and Li, D., Effects of green tea, black tea, and coffee consumption on the risk of esophageal cancer: a systematic review and meta-analysis of observational studies. Nutrition and cancer, 2013;65(1):1-16.

[36]. Sang L.X., Chang B., Li, X.H. and Jiang M., Green tea consumption and risk of esophageal cancer: a meta-analysis of published epidemiological studies. Nutrition and cancer, 2013;65(6):802-812.

[37]. Anderson Lesley A. Murray Liam J., 2013. Intakes of dietary folate and other B vitamins are associated with risks of esophageal adenocarcinoma, Barrett's esophagus, and reflux esophagitis. The Journal of nutrition, 2013;143(12):1966-1973.

[38]. Jakszyn P., Luján-Barroso L., Agudo A., Bueno-de-Mesquita H.B., Molina E., Sánchez M.J., Fonseca-Nunes A., Siersema P.D., Matiello A., Tumino R. and Saieva C., Meat and heme iron intake and esophageal adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition study. International journal of cancer, 2013;133(11):2744-2750.

[39]. O'Doherty M.G., Freedman N.D., Hollenbeck A.R., Schatzkin A., Murray L.J., Cantwell M.M. and Abnet C.C., Association of dietary fat intakes with risk of esophageal and gastric cancer in the NIH-AARP diet and health study. International journal of cancer, 2012;131(6):1376-1387.

[40]. Eslamian G., Jessri M., Hajizadeh B., Ibiebele T.I. and Rashidkhani B, Higher glycemic index and glycemic load diet is associated with increased risk of esophageal squamous cell carcinoma: a case-control study. Nutrition research, 2013; 33(9): 719-725.

[41]. Riccardi D. and Allen K., Nutritional Management of Patients with Esophageal and Esophagogastric Junction Cancer: Several strategies can be incorporated to preserve or restore nutritional status of malnourished patients during management of esophageal cancer. Cancer control, 1999; 6(1): 64-72.

[42]. Donaldson MS. Nutrition and cancer: a review of the evidence for an anti-cancer diet. Nutrition journal. 2004;3(1):1-21.