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Review Article

Phytochemicals for Cancer

Cancer Treatment with Natural Products – Phytochemicals

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Abstract: Since over forty years ago, numerous studies have been conducted on the anticancer potential of natural compounds, which have a surprising chemical variety. Society's collective endeavors have made enormous strides, introducing natural products into clinical usage and uncovering novel therapeutic possibilities, but there are still obstacles to overcome. We might have reached a turning point when we need to review the approaches to comprehend nature's products and investigate their therapeutic efficacy due to the striking changes in the landscape of cancer therapy and the expanding involvement of advanced technology. For being able to revive the search for natural goods as cancer therapies, this review highlights the major developments in natural product-centered cancer research and argues for the adoption of systematic methodologies and the development of novel pharmacological models, including the investigation of future avenues. It is because many natural products contain compounds that have been found to have beneficial effects against cancer, and these compounds can be used in combination with traditional therapies to increase efficacy and reduce side effects. Additionally, systematic methodologies and novel pharmacological models can help identify potential new therapies or combinations that would be more effective than traditional treatments. Natural products can also be used as preventive measures to reduce the risk of developing cancer. Furthermore, natural products can reduce the toxicity of traditional treatments and improve the quality of life for cancer patients. Moreover, natural products can be safely integrated into existing treatments to maximize the efficacy of treatment plans.

Keywords: Phytochemicals, Berberine, Ellagic acid, Icariin, Natural Products for Cancer, and Genistein

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1. INTRODUCTION

Cancer is the leading cause of death worldwide and is hereditary and difficult to treat. There will likely be an additional 20 million cancer cases globally in 2022. Based on the forecast, cancer will probably cause seven out of every 10 fatalities in Central and South America, Africa, and Asia[1]. Most developing nations will need to improve and establish better tactical preparedness to restrict reconnaissance, early recognition, and active treatment for cancer patients. The prevalence of cancer is increasing globally and has risen to several causes, including aging populations, expanding populations, and rapid socioeconomic development. Since there is accumulating DNA damage and numerous phases of carcinogenesis, there is a chance that cancer diseases get worse as people age[2]. In recent years, advances in innovative therapies have enhanced the cancer diagnosis rate and the overall life expectancy of cancer patients. Currently, the National Cancer Institute (NCI) defines eight areas of cancer treatment, including surgery, radiation, chemotherapy, targeted therapy, immunotherapy, stem cell transplant, and precision medicine[3]. Nevertheless, surgery, radiation, and chemotherapy are the standard methods for treating cancer. In contrast, despite the different chemotherapeutic drug types used to treat cancer and the success of multiple management programs in providing relief, the primary treatments have not produced the intended outcome. Interestingly, frequent medication resistance was seen following an initial favorable response in cancer patients. Certain earlier specific medicines demonstrated a positive clinical response. Contrary to intrinsic resistance, which develops before any cancer therapy, this shift in treatment is referred to as gained drug resistance [4]. Targeted treatments with various molecular mechanisms and cytotoxic chemotherapy contribute to acquired drug resistance. These molecular mechanisms in the majority of cancers can include redundant and compensatory molecular signaling, targeting mutations acquired during therapy, modifying the synthesis of the focused on proteins, blocking pro-apoptotic pathways, turning on pro-survival signaling, turning off DNA repair mechanisms, and upregulating tumor cell efflux transporters[5]. Considering advancements, the primary problems for individuals receiving first-line therapy include chemotherapy resistance and adverse effects. Various small molecules and inhibitors specifically target essential signaling pathways in targeted treatment. It is unusual for resistance to develop even after the initial dosage. The outcome is tumor or cancer cells being specifically selected for molecular mechanisms that may compensate for the carefully targeted route; drug resistance manifests in the patient. Due to this, it urgently needs to seek more specific and active substances or natural products that have fewer side effects, more medicinal components, are economical, and have the lowest level of disease resistance for cancer treatment. Less information, however, is available in the scientific literature about one's use of these natural compounds and their unique methods of fighting solid tumors. Natural remedies have always been significant in the treatment of human problems. Furthermore, natural materials are a significant component of modern pharmacological instruments, particularly in antibiotic and cancer treatments, and traditional medicines, often based on local plants, still regulate therapeutic practices internationally. The greatest hope for cancer treatment is an early diagnosis and complete tumor excision by surgery or radiation therapy. Contrarily, chemotherapy is typically needed for treating malignant and metastatic illnesses. According to this definition, the progression of natural product-based chemotherapeutic approaches is directly or indirectly responsible for the most notable advancements that have been acknowledged for the management of cancer[6]. Over the past several decades, mounting data has shown how effectively plant-based medicines have been amplified or used. Medical plants, such as epigallocatechin gallate (EGCG), resveratrol, curcumin, surgical, etc., have demonstrated great therapeutic potential with little side effects and low cost, in contrast to the high cost and adverse effects of most modern pharmaceuticals and even green tea contains a polyphenol called EGCG. The important source of naturally occurring chemicals with biological activity is plant-derived products. Additionally, the scientific community and physicians in contemporary medication research have taken note of their greater tolerability and nontoxic or less toxic nature to normal cells. Over six hundred natural substances have been demonstrated to be effective anticancer agents. These natural substances are being studied for their potential use as alternative therapies for cancer, with promising results. Additionally, research is currently done on natural products to improve the effectiveness of existing cancer treatments. Organic materials were determined to have anti-inflammatory, antioxidant, and immunomodulatory properties, which can help reduce the expansion and dissemination of cancer cells. Bio-based materials are being studied for their potential to treat chronic diseases such as cancer. Organic materials were found to be effective in targeting cancer cells while being less toxic to healthy cells. The use of bio-based materials has the potential to reduce the side-effects of traditional treatments, such as chemotherapy. This could lead to improved patient outcomes and quality of life. Bio-based materials are composed of natural compounds that can be used to target specific areas of the body, such as tumors. These materials are able to bind to cancer cells without damaging healthy cells, so the treatment can be more targeted and less toxic than traditional treatments. Additionally, these materials can be used to deliver drugs directly to the site of the tumor, which allows for more precise dosing and better patient outcomes.[35] They can also help to reduce side effects associated with traditional treatments and can help to reduce the risk of cancer recurrence. Furthermore, these natural substances are being investigated for their potential to help cancer patients gain and maintain remission

2. NATURAL PRODUCTS' FUNCTION IN THE TREATMENT OF CANCER

Indigenous populations have used organic remedies and botanicals in their medical establishments to forestall many ailments involving cancer throughout the dawn of time. In the USA, herbal therapy grounded in organic products was utilized to treat or protect against different diseases in around forty percent of cases[7]. Over one-half of the drugs on the market are based on organic products, which have usually served as a foundation for research into discovering innovative plant-based therapeutic agents as part of complementary medicine in the United States. Despite significant advancements in cancer prevention and therapy, there are still significant gaps that must be filled. Biosensors for Oral Cancer Detection have the potential to revolutionize early detection of cancer, allowing for earlier diagnosis and better outcomes for patients. This technology has the potential to provide a low-cost, rapid and accurate method for detecting early signs of cancer. The technology is

still in the development stage and needs to be further tested and validated before it can be used in the clinic. With further research, it could become a powerful tool that can help save countless lives. This technology uses a machine-learning algorithm that can analyze medical images and detect subtle changes in the tissue that are associated with cancer. If successful, it could enable early diagnosis of cancer, which could significantly improve patient outcomes[31]. Researchers are developing a saliva-based test for oral cancer that could be used to detect the disease in its early stages. The test measures levels of certain proteins and indicators of inflammation in the saliva. This test has the potential to be a game-changer for early detection and diagnosis of oral cancer, providing patients with a much more accessible and affordable solution. The test is currently in the early stages of development, and more research needs to be done. If successful, it could revolutionize the way oral cancer is detected and treated. It could save countless lives. If high levels of these biomarkers are detected, it could be an indication of cancer. Early detection of cancer increases the chances of successful treatment and survival.[34] Numerous research has found that the extensive use of plant-based therapeutics, like flavonoids, phenolic, alkaloids, and organosulfur compounds, with the capacity to control physiological functions has been demonstrated to prevent cancer in several in vivo and in vitro cancer models via various mechanisms. Organic objects may change many things, including physiological signaling pathways, apoptosis, metastasis, and Angiogenesis Figure 1.

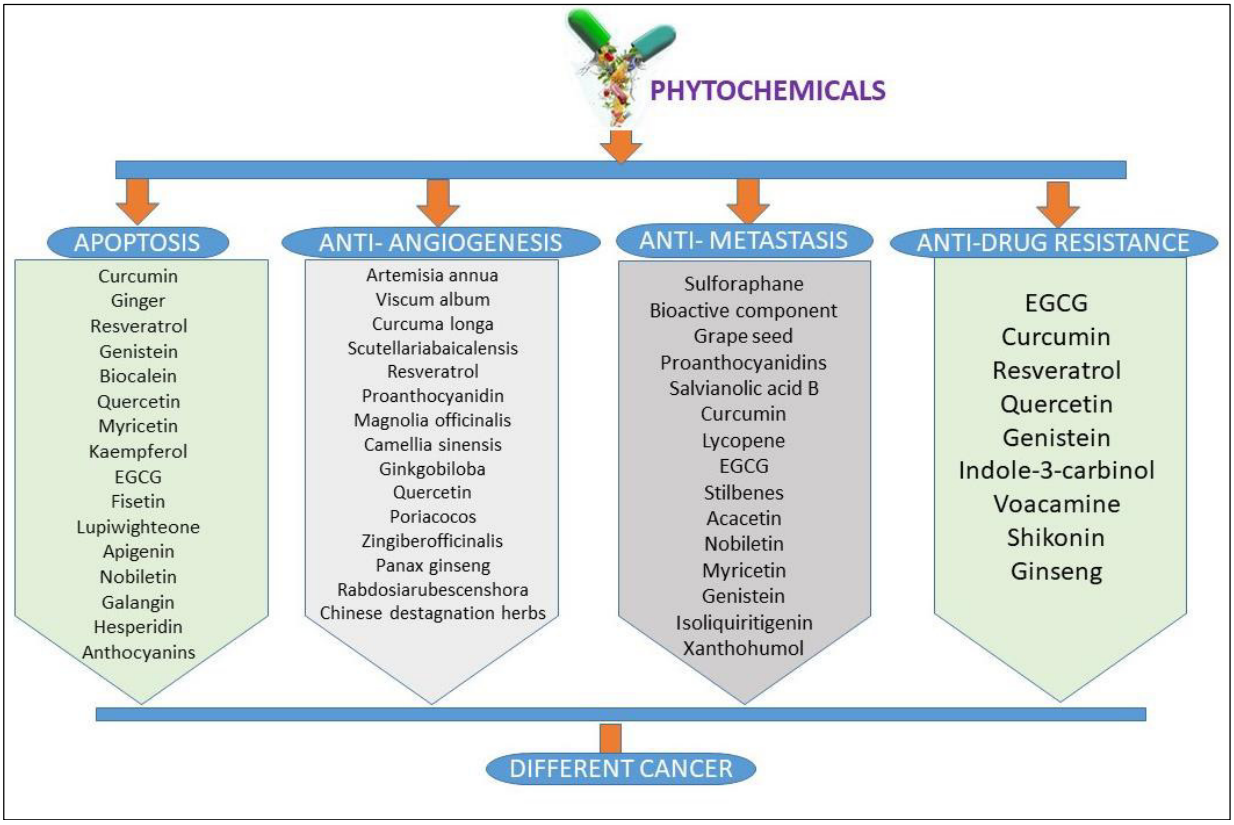

Fig 1. Pictorial representation of cellular process regulated by different phytochemicals against various cancer forms[8].

3. THE EVOLUTION OF ORGANIC PRODUCTS IN MEDICAL THERAPY

Organic elements have influenced the creation of cancer treatments throughout history. Irinotecan, paclitaxel, etoposide, and vincristine which are all frequently used chemotherapy medications, are made of organic chemicals, as are bleomycin, mitomycin C, and actinomycin D, which are all derived from marine sources[9]. Marine-derived natural bioactive compounds are organic chemicals that are derived from marine sources such as algae, bacteria, fungi, and sponges. These compounds have been shown to have anticancer properties, and are the basis of many chemotherapy medications. Many of these drugs have been used in the treatment of different types of cancer, including lung cancer, breast cancer, and leukemia. The use of natural compounds from marine sources has revolutionized the field of cancer treatment and has improved the prognosis for many patients.[30] These medications are still the mainstay of cancer therapy and will continue to be so for a long time. These organic elements have been examined to understand how they interact with melanoma cells, allowing researchers to develop more effective treatments for different forms of cancer. By understanding the chemistry of these organic elements, scientists have been able to synthesize and modify them to create new and more powerful anti-cancer agents. Moreover, these new agents have revolutionized cancer treatments, providing a much more targeted approach to fighting cancer and improving patient outcomes.

4. BERBERINE

In several cancerous cells, berberine therapy immediately raises mitochondrial elements, encourages cell cycle stalling, and starts targeted death of cells. So it is because berberine therapy can trigger inducing the cell death of malignant cells by targeting the mitochondrial membrane potential, leading to the disclosure of apoptosis-inducing factors, such as

cytochrome C and the caspases' stimulation, which are key proteins in apoptosis[10]. Additionally, it stops the cell cycle and initiates its demise by suppressing the synthesis of NF-B. It ultimately causes the cancer cells to undergo programmed cell death, thus halting cancer growth and preventing its spread[11]. Consequently, NF-B synthesis is inhibited, resulting in the cancer cells undergoing apoptosis, thereby inhibiting cancer growth and metastasis.

5. ELLAGIC ACID

Ellagic acid demonstrates anti-proliferative action and triggers apoptosis caused by the caspase enzyme[12]. By preventing the CYP1Al-dependent activation of benzo[a]pyrene, it prevents the enlargement of tumors brought on by polycyclic aromatic hydrocarbons. It means that by blocking the activation of the benzo[a]pyrene, the caspase enzyme can trigger apoptosis, which is the death of cancer cells. This action stops the cells from dividing and growing, thereby preventing the formation of tumors. In addition, ellagic acid and luteolin reduce MMP-2 and MMP-9 expression in a dose-dependent manner[13,14]. It means that these compounds can help regulate the activity of enzymes linked with the formation of cancer cells, their migration, and the creation of new blood vessels that cancer cells need to thrive. In addition, these compounds can also be meddling with the signals sent out by cancer cells that help them to survive and proliferate, further helping to prevent tumor formation. Furthermore, these compounds may help to reduce the probability of metastasis by disrupting the tumor, which can disseminate other additional organs to the body.

6. ICARIIN

Prenylated flavonol glycosides known as icaridin are obtained from the medicinal plant. Icariin triggered the Fas-mediated caspase-dependent apoptotic pathway in human hepatocellular cancer. Icariin Prostate tumor cells' ability to increase has been hindered by upregulating the amount of p16Ink4a, p27Kip1, and pRb and downregulating the production of Cyclin D1, CDK4, and phosphorylated pRb. Icariin also induced apoptosis in cells from human colon tumors via the greater manifestation of cleaved caspase-3 and PARP and the reduced manifestation of Bcl-2. In addition, icariin suppressed the expression of VEGF, MMP-2, and MMP-9 in human colon cancer cells. By targeting these specific proteins and pathways, icariin effectively inhibits proliferation, apoptosis, and VEGF expression in prostate and colon cancer cells. Moreover, icariin also inhibited human carcinoma of the colon cells' motility by preventing the manifestation of MMPs, indicating the prospect of a potent anti-cancer drug[16-18].

7. KAEMPFEROL

Fruits, seeds, flowers, leaves, green vegetables, and many plants are the sources of kaempferol. Numerous actions, including anticancer, anti-inflammatory, antioxidant, antitumor, antibacterial, neuroprotective, and cardioprotective, have been linked to it[19]. Anticancer effects of kaempferol have been observed in both in vitro and in vivo studies, with its ability to inhibit the growth of cancer cells and induce apoptosis. In addition, kaempferol has been found to possess anti-inflammatory, antioxidant, and antibacterial properties, as well as neuroprotective and cardioprotective effects when taken orally. Kaempferol has also been reported to have a potential role in sensitizing cancer cells to radiotherapy and chemotherapy. It has also been found to reduce the risk of certain types of cancer such as colorectal cancer, breast cancer, and prostate cancer[33] By acting as an estrogen receptor antagonist, kaempferol prevented breast cancer growth brought on by triclosan and E2. These findings suggest that kaempferol may hold promise as a therapeutic agent for preventing breast cancer growth, and further studies should be conducted to evaluate its potential in this capacity. Kaempferol is naturally occurring and relatively safe, making it a promising candidate for the development of breast cancer treatments. Additionally, kaempferol has been found to have a wide range of health benefits, such as anti-inflammatory and antioxidant properties. Therefore, kaempferol could be a valuable tool in the fight against cancer. Research has shown that kaempferol can inhibit the growth of breast cancer cells, suggesting that it could be a powerful weapon in the fight against the disease. It also has the potential to reduce the side effects associated with traditional treatments, such as chemotherapy. In addition, kaempferol has the potential to be used as a preventive measure, as it may help to reduce the risk of developing breast cancer.[36] According to an in vivo investigation, kaempferol inhibits murine melanoma metastasis. It was additionally discovered to have anti-angiogenic properties, which can be used to reduce the widening of tumors. And additionally demonstrated that Kaempferol increases the lifespan of fruit flies. Kaempferol also possesses antidiabetic and anti-obesity properties[20]. It is because kaempferol inhibits the activity of certain enzymes that are taking part in the widening and spread of cancer cells. It also disrupts the pathways that allow melanoma cells to grow and spread. Additionally, kaempferol has been found to reduce inflammation, reducing the possibility of cancer. Furthermore, it has been shown to lessen and boost the immune system, which can help the body fight off melanoma cells[21]. Moreover, kaempferol has been demonstrated to lower blood sugar levels and regulate weight gain, making it a potentially beneficial natural supplement for diabetes and obesity management.

8. GENISTEIN

Genistein comes from legumes like fava beans, lupin, and soybeans. Consumption of soy, lupin, and fava beans is linked to various positive outcomes[22], including a decreased risk of some malignancies, cardiovascular disease, and diabetes. In addition, Genistein has the potential against colon cancer osteoporosis and relief from postmenopausal symptoms. According to research, genistein diminishes the negative impact of epidermal growth factor (EGF) on the forkhead box O3 (FOXO3) activity in a colon cancer model, preventing tumor development and cell proliferation[23].

9. TAXOL AND CAMPTOTHE

Although camptothecin's anticancer potential was located in Camptotheca acuminata's wood and barked around the mid-sixties, it took nearly twenty years for its method of effectiveness to be discovered before it might be served as an anticancer drug. Topoisomerase I, a key player in the replication of DNA and gene transcription, may be preferentially trapped by camptothecin and bind to DNA to create topoisomerase-DNA complexes[24]. A resurgence of interest in creating camptothecin analogs with improved solubility, lower toxicity, and preserved anticancer

effectiveness resulted from this novel route of action. Taxus brevifolia bark, a limited resource that only produces a tiny amount on the subject, was initially utilized to isolate taxo[25]l. Taxol was discovered to attach to microtubules and disrupt microtubule dynamics, causing cancer cells to undergo catastrophic mitosis. In addition, Taxol was revealed to be a potent inhibitor of cell growth in numerous cancer cell lines. Its potential for selectively targeting cancer cells made it an attractive target for further research[26]. This research has led to the development of several synthetic analogs of taxol with improved solubility, lower toxicity, and maintained anticancer effectiveness. These analogs are now being used in various treatments for different types of cancer. By combining the advantages of taxol with those of its synthetic analogs, these new treatments offer a promising outlook for cancer patients.

10. DRUG SEARCHING FOR SPECIFIC MOLECULES IN NATURAL PRODUCTS

The current state of treatment for cancer is evolving as an outcome of expanding molecularly directed medicines. The search for molecularly targeted drugs has captured the attention of organic product researchers as the area matures. Broad-spectrum protein tyrosine kinases ought to be ATP competitively inhibited by hematoxylin and its equivalents from the heartwood of Haematoxylon campechianum, having the greatest potency of IC_{50}s-Figure-02, on the nanomolar scale[27]. These results provide encouraging perspectives on the potential of hematoxylin and its equivalents as inhibitors of broad-spectrum protein tyrosine kinases for dental nanomaterials. The effects of hematoxylin and its equivalents on dental nanomaterials need to be further investigated in order to determine their full potential as inhibitors. Additionally, the long-term implications of hematoxylin and its equivalents on nanomaterials should be explored. This could lead to the development of more effective and targeted treatments for diseases related to dental nanomaterials. Furthermore, understanding the effects of hematoxylin and its equivalents on nanomaterials could lead to the development of safer and more effective dental products[32]. It has been shown that the substance eucalyptin A, produced from the fruits of the Eucalyptus globulus Labill, a shrub extensively distributed in southwest China, has a strong inhibitory impact on the HGF/c-Met axis. Furthermore, a study showed that the active components in Eucalyptus globulus Labill could reduce the logging on of the Ras-Raf-Mek-Erk signaling pathway[28]. As an outcome, cell growth and migration are inhibited. Additionally, it has a positive effect on suppressing tumor growth. The active components can suppress the showdown of key genes that play a part in the movement and proliferation of cells, including the Ras-Raf-Mek-Erk pathway. Additionally, the active components can prevent the growth of certain types of tumors by inhibiting the showdown of specific genes. Further, the active components can prevent cancer transitions, as they can prevent the utterance of tumor-promoting genes.

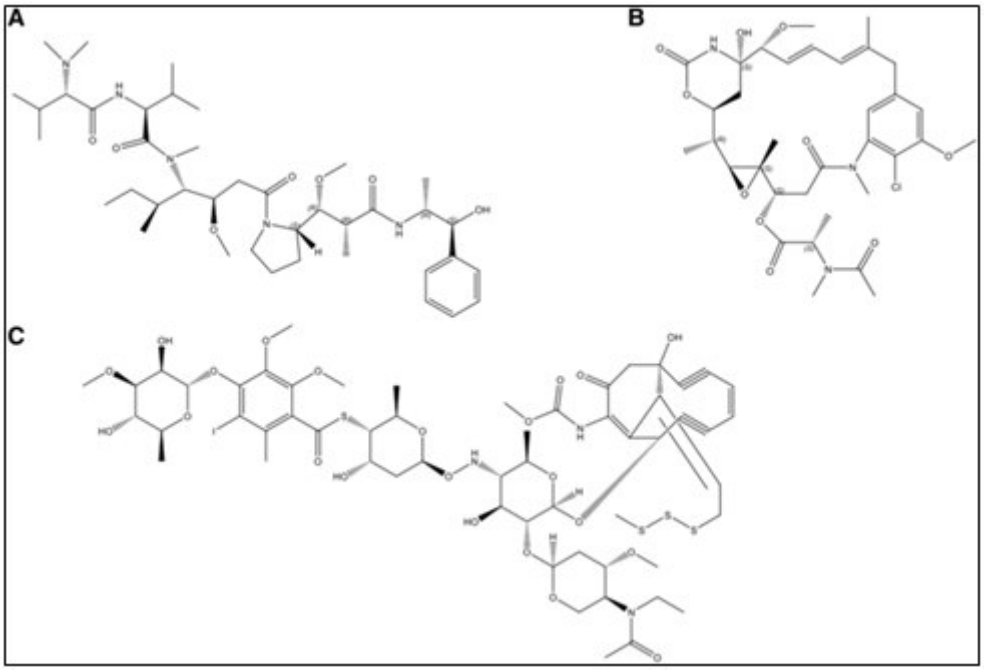

Fig 2: The chemical structures of natural products used in ADCs. a Auristatin E, the warhead molecule for MMAE; b Maytansine, the warhead molecule for DM1; c N- acetyl- calicheamicin γ , the warhead molecule for gemtuzumab ozogamicin and inotuzumab ozogamicin[29]

11. CONCLUSION

Scientific research is urgently needed to find new ways to treat solid cancers. Conventional treatments, such as surgery, radiation therapy, and chemotherapy, can be effective in some cases, but the five-year survival rate for solid cancer patients is still low. Chemotherapy often causes drug resistance and toxic side effects. In recent years, there has been a shift towards the development of natural plant-based drugs that are less toxic and have multiple targets. These drugs typically work by triggering apoptosis (cell death) or inhibiting cell proliferation. More research is needed to discover new and effective natural chemopreventive compounds. We believe that natural antitumor active ingredients and precursor drugs could provide alternative or adjuvant treatment strategies for solid cancer patients.

12. AUTHORS CONTRIBUTION STATEMENT

Conceptualization, methodology, original draft preparation, article writing, visualization, review, and editing, Dr M.R.Suchitra; software work, validation, data curation, review, and editing, Ranjeet Kumar Chourasia, Vidhya Rekha Umapathy, A.Vinita Mary, Dr.Kesavan. R and Dr. Ranjani.D; resources, review and editing, supervision, project administration, and funding acquisition, Dr M.R.Suchitra, Ranjeet Kumar Chourasia. All authors have read and agreed to the published version of the manuscript.

13. CONFLICT OF INTEREST

Conflict of interest declared none.

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