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ISATIN AND IT'S DIVERSIFIED PHARMACOLOGICAL ACTIONS ON ANTICANCER THERAPY.

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Abstract:

Heterocyclic compounds play an important role in medicinal chemistry and are used in many drugs. Due to their unique structure and properties, they are versatile and valuable for drug design. For anticancer research they offer a great deal of flexibility and flexibility. However, just like any potential anticancer drug, heterocyclic compounds have drawbacks and limitations.derived compounds offer a promising pathway for the development of new anti-cancer drugs. Their diverse structural properties, low toxicity, and ability to interact with important receptors involved in the transduction and metabolic regulation of cancer signals make them attractive targets for further research. derivatives potential as potent anti-cancer drugs is supported by synthesis, characterization and assessment using a broad range of biophysical techniques, in-silico modeling and in-vitro/in vivo assays. derivatives may be safer alternatives to conventional chemotherapy drugs such as cisplatin due to their lower safety profile and improved efficacy. In conclusion, this abstract provides information on the anticancer therapeutic potential of and derived compounds.

Key word: Anticancer,Radical scavenging, Heterocyclic compound,Chemotherapy.

1. Introduction:

On February 1st, 2022, World Cancer Day, the IARC released its 2022 report. The report provides a comprehensive overview of the global cancer burden, based on a study of 115 countries. The report states that 20 million new cancer cases occurred in 2022 (compared with 19 million cases in 2020), and 9.97 million deaths occurred (compared with 9.96 million in 2020). The report estimates that 1 in every 9 men and 1 in every 12 women will die from cancer. Global cancer statistics, 2022: increasing incidence and dramatic inequalities. The global cancer incidence and mortality figures show significant differences between countries with and without higher incomes, and a significant increase in the number of new cancer cases expected in countries least prepared to cope with them.

Hetero-cyclic compounds are a significant group of organic substances with intriguing pharmacological and biological characteristics.[1], [2] A biologically active heterocyclic moiety that goes by the names indenedione and indolequinone is (1H-indole-2,3-dione). At positions 2 and 3, there are two carbonyl groups, and at position 1, there is a nitrogen atom. There are two cyclic rings in it. [3][4] which has six members in one and five in the other. The two rings have the same plane. Whereas the five-membered ring has an anti-aromatic character, the six-membered ring has an aromatic character.

Using nitric and chromic acids, Erdmann and Laurent were the first to isolate as an oxidation product of indigo. It crystallizes from acetic acid, alcohol, or water as orange-red monoclinic prism crystals that melt at 200 degrees Celsius. In people, it is a substance that comes from the parotid gland of Bufo frogs and is a metabolic byproduct of the hormone adrenaline. Other naturally occurring derivatives are found in plants. Melosatin alkaloids, such as methoxy phenylpentyl s, were extracted from Melochia tomentosa, a plant known to cause tumors in the Caribbean. Additionally, 5-(3′-methylbut-2′-yl) was extracted from Chaetomium globosum, and 6-(3′-methylbuten-2′-yl) was discovered in Strep-tomyces albus. Medicinal chemists are highly interested in and its substitutes because they exhibit a variety of biological activities, such as anticonvulsants, and a broad range of biological activities.antimicrobial,[6][7] antitubercular, antiviral, and anti-inflammatory properties. One effective chemical antiviral is

methiazone[11][12],these are the agents which possess the N-methyl group. 3-thiosemicarbazones' N-Mannich bases have demonstrated strong antibacterial activity against gram-ve bacteria and fungus. It has been reported that a number of indole derivatives have promising pharmacodynamic properties, including antidepressant, analgesic, and anti-inflammatory properties. There are also reports of antibacterial, anti-inflammatory, and antidiabetic effects from thiazole and its derivatives.[14][15]

According to the current study, drug molecules with as a pharmacophore may exhibit a wide variety of pharmacological characteristics. The chemical compound has the formula C8H5NO2. It is a derivative of indole, with an oxindole ring fused to a benzene ring in its structure. is a compound with a wide range of applications in organic synthesis, such as the production of medicines, fragrances, and dyes. It is a common starting material for the synthesis of numerous biologically active compounds and is also well-known for its intriguing biological activities.One substance whose possible medical uses has been investigated is . Its numerous biological qualities, such as its potential as an antioxidant, antiviral, antibacterial, antifungal, and anticancer agent, have all been studied. In preclinical studies, and its derivatives have demonstrated activity against a variety of cancer cell lines and pathogens, yielding encouraging results. One substance that has demonstrated promise in cancer research is . It is a naturally occurring substance that is present in many different types of plants and has been researched for possible anti-cancer effects. The potential of and its derivatives to stop tumor growth, trigger apoptosis (programmed cell death), and stop cell division in a variety of cancer types, such as leukemia, breast, lung, and colon, has been studied. Current studies are being conducted to develop potential therapeutic applications for and to learn more about the mechanisms underlying its anti-cancer effects.

The chemical compound has the formula C8H5NO2. It is a yellow, crystalline solid that dissolves in ethanol, diethyl ether, and hot water. has a number of physical characteristics:

usually takes the form of yellow crystals in appearance.

Odor: It has a distinct smell.

Melting Point: has a melting point of between 200 and 201°C.

is soluble in ethanol, diethyl ether, and hot water, but it is comparatively insoluble in cold water.

Density: has a density of about 1.34 g/cm3. can be sensitive to light and air, but it is stable in normal circumstances.It is used in many disciplines, including chemistry and medicine, and is well-known for a broad range of biological activities.

2. Scope of the Work:

Isatis tinctoria (Europe and China), Couroupita guianensis Aubl (Central America and Amazon region), Melochia tomentosa (United States, Mexico), and Boronia koniamboensis (New Caledonia) species are global sources of (1H-indol-2,3-dione), a naturally occurring alkaloid that is extracted as a reddish-orange powder from plants in the genus Isatis. (Da Silva et al., 2001; Bayly et al., 2015). The indolic compounds found in those plants have demonstrated medicinal properties and are currently being used as antineoplastic and anti-inflammatory agents. can also be found in the secretions of the Australian mollusc Dicathais orbita and the Bufo frog from Europe, North Africa, and Asia (Esmaeelian et al., 2014). Furthermore, it is an endogenous substance found in humans, primarily distributed in the central nervous system (CNS), where it is found as a metabolite of either tryptophan or epinephrine (Kerzarea and Khedekar, 2016). is a multifunctional molecule that serves as the starting point for a vast array of derivatives with the oxindole moiety and a variety of biological and pharmacological characteristics. Several reviews regarding its synthesis and potential uses have been documented in the literature. With a peculiar comprehensive diversity in their structures, derivatives have been developed for a wide range of activities, including anticonvulsant, anti-stress and anxiogenic, antiviral, antimicrobial, antitubercular, antimalarial, antifungal, antibacterial, and particularly as antitumor agents. A few derivatives have been approved as anticancer medications, while others were created and tested against cancer in clinical trials. Others were recently reported to be inhibitors of β-amyloid aggregation and cholinesterase, and potentially active in metabolic diseases (diabetes). With a focus on their anticancer properties, we aim to report here on a wide range of biological and medicinal properties of -based compounds. Several derivatives, with various substituents at any

site of its core structure, have been synthesized with the goal of producing potent and selective medicinal agents. Positions at C3 (substituent A) and C5, C6, or C7 (substituents D) in the aromatic ring seem to be the most promising ones. A variety of substituents at N1, C3, and any C in the benzene ring provided a modulation in their properties. Thus, during the past few decades, various compounds such as imines, hydrazones, thiosemicarbazones, oximes, and spiro-oxindoles have been prepared, characterized, and their biological properties assessed. Numerous reviews have been written, covering many facets of this class of compounds' chemistry, particularly those pertaining to their pharmacological and medicinal properties. However, the field is still being thoroughly researched, with numerous advancements.

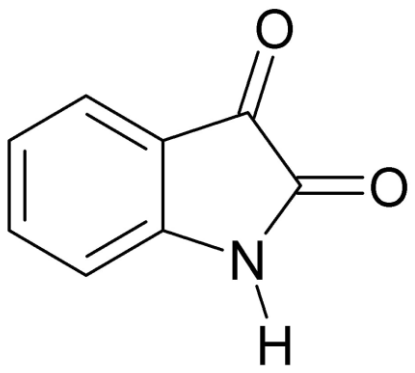

Figure1: : 1-H Indole, 2,3 Dione.

3.Natural sources of :

, a chemical of wide pharmacological uses, has many natural sources. It is found in marine organisms, tinctoria L., and Couroupita guianensis Aubl., besides being produced by mammals and humans [1] [2]. Finally, the tree Couroupita guianensis Aubl. from where is isolated is called Cannonball tree [3]. A number of studies have shown that s obtained from Couroupita guianensis Aubl. have ability to kill a range of bacterial and fungal strains which gave it therapeutic significance [4]. Owing to these facts we can say that there are vast quantities of it for use in synthesizing various drugs obtained directly from nature’s stores.

4.Chemical properties :

Isatin is also known as 1H-indole-2,3-dione, is a heterocyclic organic molecule with the chemical formula C8H5NO2. Certain plants naturally contain this peculiar crystalline solid. possesses a variety of fascinating chemical properties, including: has two groups: a keto group (-C=O) and an imine group (=NH). These are its acid-base properties. Depending on the type of reaction, it may behave as a weak acid or weak base. Protonation and deprotonation reactions are conceivable.

4.1 Acid-Base Properties: is composed of two groups: the keto group (-C=O) and the imine group (=NH). Depending on the type of reaction, it may behave as a weak acid or weak base. Protonation and deprotonation reactions are conceivable.

4.2 Electrophilic Reactions: Because of its electron-rich indole ring, is susceptible to electrophilic aromatic substitution reactions. It might pass via Friedel-Crafts.

4.3Nucleophilic Substitution Reactions: It is possible for 's carbonyl group to participate in nucleophilic addition reactions. Various nucleophiles may cause this to occur, leading to the production of distinct products. For instance, it can react with primary amines to produce N-substituted derivatives known as s or oxindoles.

4.4 Oxidation: may oxidize under certain conditions, forming new compounds as a consequence. It can undergo oxidation to yield a number of derivatives.

4.5 Reduction: Reduction processes, particularly those involving the carbonyl group, can also affect . Reduction is a useful technique for creating a wide range of compounds, including dihydros and indole derivatives.

4.6 Metal Complexation: can coordinate with metal ions to form metal complexes. These complexes often exhibit unique chemical and physical properties in contrast to free .

5. Biological Activity: In addition to having antiviral, anticancer, and antibacterial properties, and its derivatives exhibit a wide range of biological activities, including the capacity to block enzymes. These roles are often linked to its ability to interact with multiple biological targets, such as enzymes, receptors, and nucleic acids.

6. Mechanism of Action:

Numerous activities, such as antiviral, anticancer, antimicrobial, and enzyme inhibitory qualities, have been studied for and its derivatives. Especially when considering its biological and pharmacological effects, the exact target or pathway that interacts with can affect its mode of action.[21][22] Some examples of 's mechanisms of action are listed below.Numerous plants naturally contain a substance called , which has been researched for potential use in cancer treatment and prevention. It's important to keep in mind that research is still ongoing to identify the exact mechanism of action (MOA) of in cancer prevention. is a naturally occurring substance present in a wide range of flora and fauna. Its possible anticancer effects have been researched.[23] Although the precise mode of action of in cancer remains incompletely understood, certain research indicates that it could operate via multiple pathways:

6.1 Induction of apoptosis: It has been demonstrated that causes cancer cells to undergo apoptosis, or programmed cell death. This may contribute to inhibiting the spread of cancerous cells.

6.2 Inhibition of cell proliferation: It's possible that inhibits the fast growth or multiplication of cancer cells.[24] This may assist in shrinking tumors and stopping their spread.

6.3 Antioxidant activity: Because possesses antioxidant qualities, it can aid in defending cells against harm from free radicals. Extremely reactive molecules known as free radicals have been linked to the onset of cancer.[25][26]

6.4 Inhibition of angiogenesis: Additionally, may prevent angiogenesis, the process by which tumors create new blood vessels in order to get oxygen and nutrients. may aid in starving and restricting the growth of tumors by blocking angiogenesis.

6.5 Modulation of signaling pathways: may alter a number of signaling pathways that are important in the initiation and spread of cancer. In doing so, it may disrupt the processes that propel the development of cancer. All things considered, current review indicates that may be a promising substance for the creation of innovative anticancer treatments, even though more investigation is required to completely comprehend the mechanisms of action of this compound in cancer

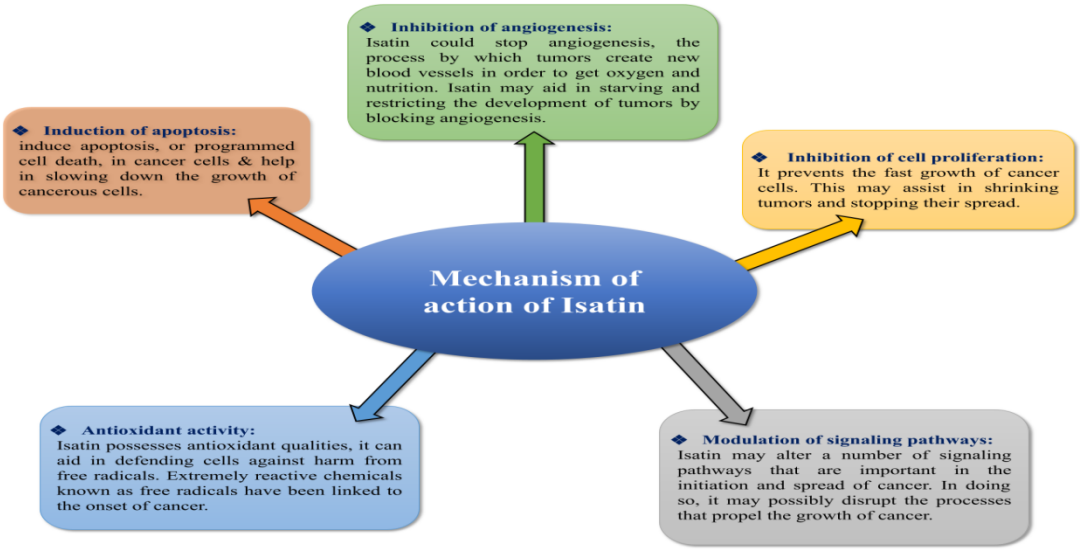

Fig: 2 Mechanism of Action of

7. Current status of cancer worldwide:

According to the IARC, there will be 20 million new cases of cancer globally in 2022, and the disease will claim 9.7 million lives. Lung and breast cancer are the most common types of cancer. High- and low-development index (HDI) countries have different cancer burdens and mortality rates. According to estimates from the International Agency for Research on Cancer (IARC), 1 in 5 persons worldwide will get cancer at some point in their lives, and 1 in 8 men and 1 in 11 women will pass away from the illness. According to these updated estimates, over 50 million people are still alive after receiving a cancer diagnosis five years ago. Global population aging and socioeconomic risk factors continue to be the main causes of this increase.The International Agency for Research on Cancer (IARC) released its 2022 report ahead of World Cancer Day on February 1. The report provides a comprehensive overview of the global cancer

burden based on a survey of 115 countries. The study found that there were 9.7 million cancer deaths (9.96 million recorded in 2020) and 20 million new cases of cancer (compared to 19.6 million in 2020). According to estimates, 1 in 9 men and 1 in 12 women will die from cancer. IARC warns that although previous projections from 2020 were based on different methodologies, these numbers represent estimates for 2022 based on the most up-to-date data and might not necessarily point to a trend.Furthermore, it is predicted that there will be over 35 million new cases of cancer in 2050, a 77% increase from the 20 million cases in 2022. Low HDI countries have seen the largest proportionate increase in incidence (up 142%), followed by medium HDI countries (up 99%). By 2050, the cancer death rate in these countries is predicted to nearly triple.

8. SAR of ISATIN:

8.1 Electron-donating and electron-withdrawing groups: Substitution at various sites on the core of can drastically alter its biological activity. For example, it has been demonstrated that groups that donate electrons, such as alkyl groups, can enhance anti-inflammatory properties, whereas groups that take electrons, such as halogens, at the 5-position of , may enhance anticancer activity.

8.2 Substitution at the 3-position: Substitution at position three may affect 's interaction with biological targets. For example, it has been shown that derivatives have greater antibacterial activity when amino groups are substituted.

8.3 Ring fusion: Fusing additional rings to the core allows for the production of compounds with a wide range of applications. For instance, adding a benzene ring to the core of can enhance its anti fungal properties.

8.4 Stereo chemistry: The stereo chemistry of derivatives may affect their biological activity. For example, some derivatives interact stereo specifically with enzymes or receptors.

8.5 Functional groups: Certain functional groups, such as carboxylic acid groups or hydroxyl groups, can also affect the biological activity of derivatives.

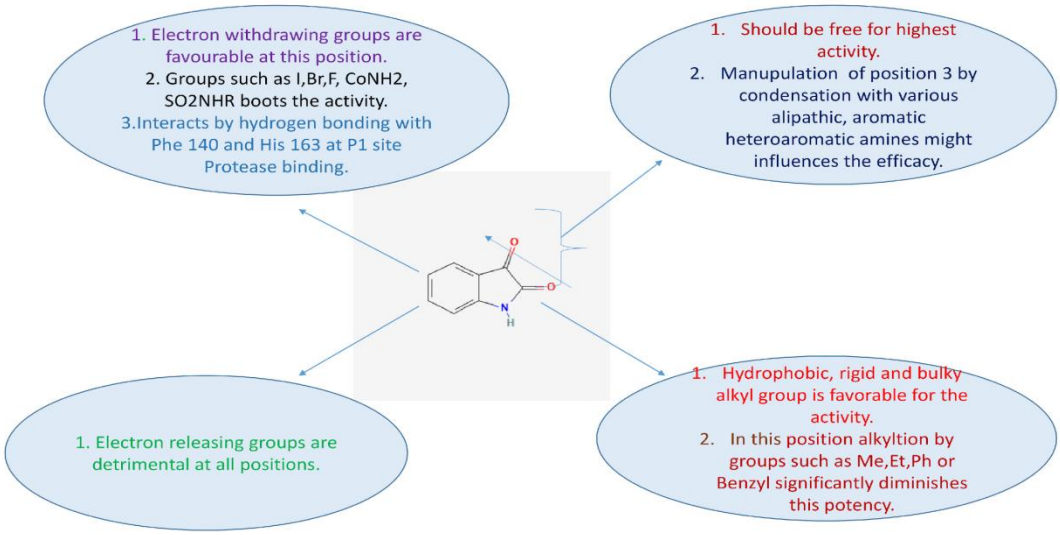

Fig:3 Structural activity relationship of

9. In anticancer therapy:

In 2019, Xu et al. [10] reported the anti tumor efficacy of benzofuran– hybrids connected through pentylene and hexylene. The anticancer activities of the obtained hybrids were investigated using CCK-8 Assay Kit against human cancer cell lines A549, HepG2, MCF-7, PC-3 and HeLa. Compounds among the most active analogues against the tested cell lines were 14g – IC50 77.2-88.9 μM and 14h – IC50 65.4-89.7 μM.SAR analysis reveals that the anticancer activity is dramatically influenced by substitution on the moiety and benzofuran motif at the C-3 and C-5 positions. The electronegative atom -F is containing . The potency could improve when at the benzofuran motif and the C-5 position of include the electron-withdrawing group, but the anticancer activity was reduced. Compound 15i also has a broad-spectrum anticancer effect against A549, HepG2, SF-268 cancer cell lines, with IC50 ranging from 78.1 —90.7 μM, whereas the reference vorinostat had an IC50 of 71.1 to > 100 μM.According to the SAR and in vitro findings, the activity and the fluoroquinolone framework are closely combined. Methyl substituent at the nucleus's C-3 position might give it a boost. The electron-donating methyl C-5 was found to enhance its activities, whereas the electron-withdrawing fluoro substitution was risky. In 2019, Zhang etal. [11][27] evaluated the anti tumor potential of eleven new

ciprofloxacin/gatifloxacin-1,2,3-triazole- analogues. The anticancer potential was assessed using a CCK-8 Assay Kit on human cancer cell lines A549, HepG2, MCF-7, PANC-1, and SF-268. Most hybrids that were synthesized were effective against SF-268, HepG2, and A549 cancer types.Evaluation of antiproliferative efficacy: In 2020,Al-Wabli etal. determined the antiproliferative efficacy of novel -based conjugates on the cell lines HT-29, ZR-75, and A-549 . The preparation of conjugates enabled to identify remarkable in vitro antiproliferative efficacy of compound 16m against all investigated human cancer cell lines. Its average IC 50 values were 1.17 µM, which was approximately seven times greater than that of the reference drug, sunitinib – IC 50 would be 8.11 µM . Further analysis confirmed the reduction in the amount of cells in the G2/M and S phases while the number of cells in the G1 phase increased . Moreover, compound 16m strongly enhanced BAX expression, stimulated caspase-3 activation and reduced the quantity of phosphorylated RB demonstrated by:the rise in cleaved caspase-3 levels that was seen. From the acquired results, the SAR study showed the moiety substituted with an N–benzyl ring seems to be fortunate for antiproliferative activity[19][20]

9.1 In colon cancer:

Preliminary study on the subject of colon cancer indicates that derivatives of Isatin could inhibit the growth of colon cancer cells. Nevertheless, further research is required to completely comprehend the therapeutic potential of Isatin and its derivatives in the treatment of colon cancer, including in vivo investigations and clinical trials.The bis methane synthesis process[44][45] was modified to create the 5-fluoro-3-hydroxy-3- (1H-pyrrole-2-yl) indolin-2-one.[46][47] . Additionally, the compound's bioactivity against WiDr colon cancer cells was examined. According to reports, isatin with substituents in C3 has the highest percentage of synthesis, resulting in the highest demonstrated biological activity.[48][49] One pertinent example of a chemical with C3 replaced is sunitinib. Sunitinib has the ability to prevent HT-29 colon cancer cells from synthesizing HIF-1á. 1-[2-(3,5-diaryl-4,5-dihydropyrazol-1-yl)-2-oxoethyl] synthesized- 1H-indole-2,3-diones 1a, 1b, 1d, and 1,3-dihydroindol-2-one conjugates containing 4-thiazolidinone moieties (2d–2f, 3a, 3c, and 3d) and 3,5-diaryl–4,5-dihydropyrazolyne were submitted and assessed at a single concentration of 10^5 M against a

variety of about sixty cancer cell lines, including colon cancer.Conversely, diazoles, which include pyrazoles and pyrazolines, have had a special place in the creation and synthesis of new biologically active substances with impressive anticancer properties.[51][52] The human breast cancer cell line MDAMB-231 and the colon cancer cell line LOVO were used to test the anti-tumor activity of a number of quinazolinone compounds that included the isatin moiety during their synthesis[53][54].It has been reported that analogues with an α,β-unsaturated ketone moiety may be anti-cancer agents.[56][57]It has been reported that benzofuran and a few of its derivatives are cytotoxic and may be used as colon cancer treatments.Several studies have looked at tryptophan potential as a colon cancer inhibitor as well as its essential role in halting the growth of tumors and cancer cells[58][59]. According to these investigations, tryptophan inhibits colon cancer cells in a highly specific manner.Electron-withdrawing groups like halogens and nitro at position 6 enhance antibacterial and anti-cancer activities. Halogens were also discovered to be an essential substitution at position 7 that can improve bacterial infection caused by Gram-positive pathogens.Wagdy M. Eldehna et al have designed and synthesized a novel series of benzofuran- conjugates linked by a carbohydrazide group. [62][63][64]All were selected according to NCI's DTP selection guidelines for the assessment of their anti tumor activity against NCI-55 human cancer cell lines. All compounds proved effective against diverse cell lines.In addition, the novel conjugates of the study showed good anti-proliferative activity against two human colorectal cancer cell lines.[15][65][66] B Prayitno1 and M Santoso2l have designed and synthesized Biochemical activities of new derivative against WiDr colon cancer[16]

9.2 In breast Cancer:

In addition to its many medicinal applications, (IST), an endogenous molecule that is a member of the primary class of heterocyclic compounds,[68][67] may be used as a building block to create additional pharmacological chemicals.[27][28][69] The many pharmacological properties of IST derivatives have previously been extensively documented in the literature, most notably their anticancer properties. Commercially available IST-derived compounds are also used to treat other cancers, including as renal cell carcinoma (RCC) treated with sunitinib and

cryptogenic fibrosing alveolitis treated with nintedanib. However, their efficacy in treating BC was not shown.Garima Chauhan et al. employ MCF-7, MDA MB 231, MDA-MB 435, and MDA-MB 468 cell lines to predominantly study the anti-BC capabilities of IST derivatives. Using MCF-7 and MDA MB 231, MDA-MB 435, and MDA-MB 468 cell lines, they established the anti-BC effects of several IST analogues.[29][30]]70].It has also shown the powerful compound of the series and the structure-activity connections of compounds using molecular docking. Thus, the primary finding of this study is the significance of IST as a primary resource for drug design and the creation of novel anti-BC medications Fifteen butyric ester tethered DHA- hybrids have been developed, synthesized, and analyzed by Shijia Zhao et al. for their antiproliferative ability against MCF-7, MDA-MB-231, MCF-7/ADR, and MDA-MB-231/ADR breast cancer cell lines. While ethoxime enhanced the activity against MCF-7 cancer cells, skeleton was advantageous for the activity against MDA-MB-231 and MDA-MB-231/ADR breast cancer cell lines.[72][73] Overall, the study found that the butyric ester tethered DHA-hybrids showed promising antiproliferative effects on various breast cancer cell lines.[31][32] These findings suggest potential for further development of these compounds as anticancer agents. The study also indicated that the DHA- hybrids exhibited selectivity towards cancer cells compared to normal cells, highlighting their potential as targeted therapies [13][74][70]. Further research is needed to explore the mechanisms of action and optimize the efficacy of these compounds for clinical applications.[33][34]

9.3 In lung Cancer:

Because hybrids created by fusing or conjugating distinct active pharmacophores may affect several targets, they have the potential to improve efficacy, overcome drug resistance, and minimize negative effects[35][75][76]. Rupesh K. Mishra that both dihydroartemisinin and have strong anti-lung cancer properties, it is possible that hybridising the two compounds will result in novel anti-lung cancer options.[36]When ferrous ions are present, dihydroartemisinin (DHA) with a distinct sesquiterpene endoperoxide lactone moiety can produce extremely reactive free radicals; in contrast, cancer cells have 1,000 times higher concentrations of FeII than normal cells.[14] Haodong Hou, Bin Qu, Chen Su, Guihua Hou, and Feng Gao said as a result, DHA

clearly inhibited the growth of lung cancer cells,[37][38] such as large cell lung carcinoma, lung adenocarcinoma, and lung squamous carcinoma, without significantly harming healthy cells.[39]

9.4 In Liver cancer:

The research on specifically for liver cancer is limited, and more studies are needed to fully understand its effects and potential as a therapeutic agent for this type of cancer. It's important to consult with healthcare professionals before considering any new treatment options, including those involving or its derivatives, for liver cancer.[78][79]

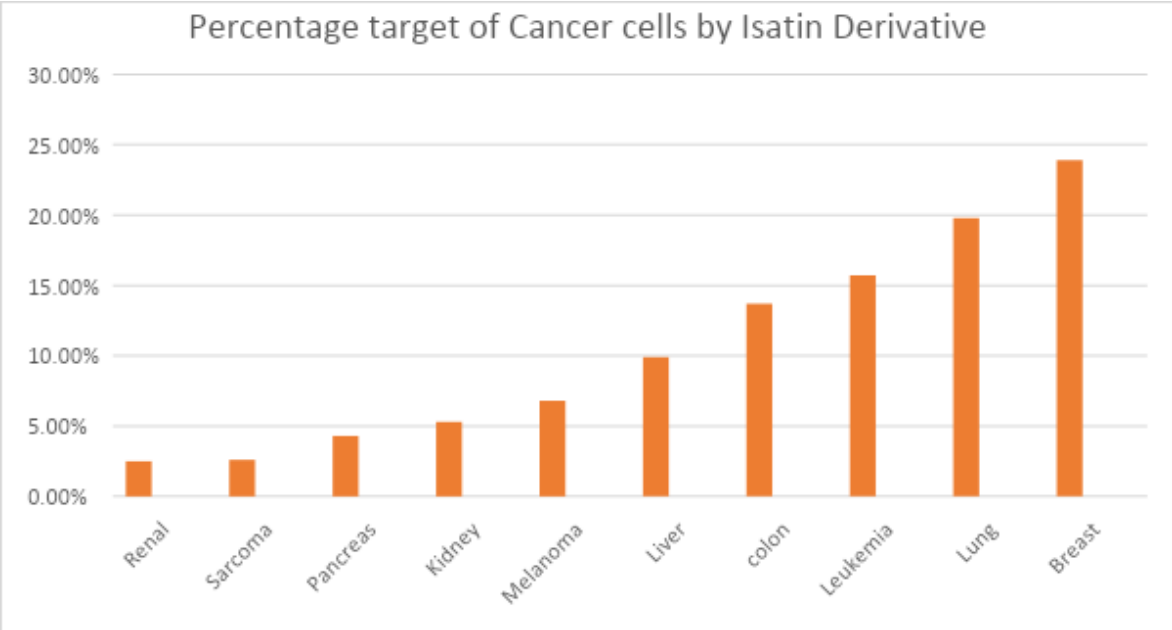

Fig:4 Target percentage of Cancer cell by derivatives [91]

10. Market share & Future prospect:

has bright future potential as a cancer treatment, but further study and advancement are needed. In preclinical research, and its derivatives have shown intriguing anticancer effects, such as inducing apoptosis, arresting the cell cycle, and preventing angiogenesis[40] and metastasis in a variety of cancer types.Improving the efficacy and selectivity of derivatives against cancer cells while reducing side effects is one of the main difficulties.[41][42] Scientists are investigating

methods to alter the molecular structure of in order to enhance its pharmacokinetic properties, bio availability, and capacity to target cancer cells.To improve effectiveness and combat medication resistance, combination treatments combining derivatives with other anticancer drugs are being researched. These methods may eventually result in the creation of fresh, more potent cancer patient remedies.An expert and thorough analysis of the present status of the global market, with a focus on the Chinese market, is provided in 2024 Global and Chinese Market Size, Share & trends Analysis.[43][18] Important market data for is provided in the research. For businesses and people interested in the industry, it is an invaluable source of direction and advice.It is anticipated that the market would continue to grow significantly between 2023 and 2031. Recently, there has been a rapid and notable expansion in the market. Strong growth rates are foreseen throughout the projected period because of the favorable momentum in market dynamics and the anticipated sustained expansion. In summary, the market is poised for significant and noteworthy expansion. The Market has had rapid and notable growth in the last few years.[44][48] Predictions for the market's huge expansion between 2023 and 2031 indicate a stable upward trend in market dynamics and strong growth rates in the near future.[80][81]

11.Acknowledgement

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