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Scientific landscape of melatonin, its hybrids, and its derivatives as anti-tumor agents: A bibliometric analysis

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ABSTRACT

Melatonin (MLT), its derivatives, and its hybrids have been marked beneficial against several human malignancies by inhibiting the growth of different tumors not only under both *in vitro* and *in vivo* conditions but also, specially MLT, for the management of cancer in clinical trials. In this study, a bibliometric analysis of peer-reviewed scientific literature on MLT, as well as their derivatives and hybrids published from 1973 to 16 August 2023 is presented. A total of 2792 articles retrieved in Scopus were analyzed and visualized by VOSviewer 1.6.19. The records show a rise in the number of published papers since 2004. In addition, the main areas of knowledge in which the researchers concentrated the studies were: (i) Biochemistry, Genetics, and Molecular Biology, (ii) Medicine, and (iii) Pharmacology, Toxicology, and Pharmaceutics, with 33.9, 32.4, and 10.1% of the records, respectively. Molecular docking studies of MLT and their anticancer activities for several types of cancer appeared as one of the hotspots of this field. The top five most productive countries—in terms of number of published articles—in studies associated with MLT are the United States, China, Italy, Spain, and Germany.

INTRODUCTION

Cancer remains one of the main causes of morbidity and mortality in the world [1], and although it has been considered one of the most preventable diseases, its incidence continues to show an increasing trend. In line with global trends, according to the GLOBOCAN database report for the year 2022, this pathology was the second cause of death exceeded only by cardiovascular diseases, accounting for nearly 10 million deaths by 2020 for men and women combined [2]. Global patterns show that lung cancer was the leading cancer accounting for 18% of all cancer deaths, followed by colorectal (9.4%), liver (8.3%), stomach (7.7%), and female breast (6.9%) cancers.

Although the drugs currently used in cancer therapy prevent the transformation of pre-malignant cells into adenomas, and ultimately into carcinoma, their use can lead to resistance, as well as significant systemic toxicity with effects such as neurotoxic, gastrointestinal disorders, alopecia, renal dysfunction, hypertension, and skin toxicity. In addition, most cancer patients eventually suffer from cachexia and anorexia during the course of the disease leading to metabolic dysfunction, suppression of the immune response, emaciation, weakness, and fatigue with a significant impact on quality of life [3]. In this scenario, promising therapeutic alternatives for treating various cancers have been investigated. The fruit of these efforts, emerging drugs, such as melatonin (MLT), which have demonstrated great potential to combat various types of cancer (Fig. 1A). MLT (*N*-acetyl-5-methoxy-triptamine), is an endogenous neurohormone synthesized by the pineal gland. MLT plays a very critical role in determining homeostasis, neurohumoral stability, and regulation of circadian rhythms in synergy with other hormones and neuropeptides. The biological properties of MLT range beyond circadian rhythm regulation. MLT has received increasing attention in recent years because

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of its versatile regulatory actions as a dietary supplement or medication growing in popularity in the pharmaceutical market as an antioxidant, anxiolytic, antihypertensive, sedative, analgesic anti-inflammatory, neuroprotective effects, and of particular interest in this paper, the ability to prevent, treat, and delay tumor development [4–6]. Regarding the relationship between the structure of MLT and its antitumoral effects, a recent SAR study has demonstrated that the *N*-acetyl side chain plays a crucial role in the antiproliferative and oncolytic effects of MLT because removal of the *N*-acetyl group produces an important loss of cytotoxic response. The role of the 5-methoxy group is to potentiate the antiproliferative effects of MLT, while the tryptamine core is mostly responsible for its anticancer benefits [7].

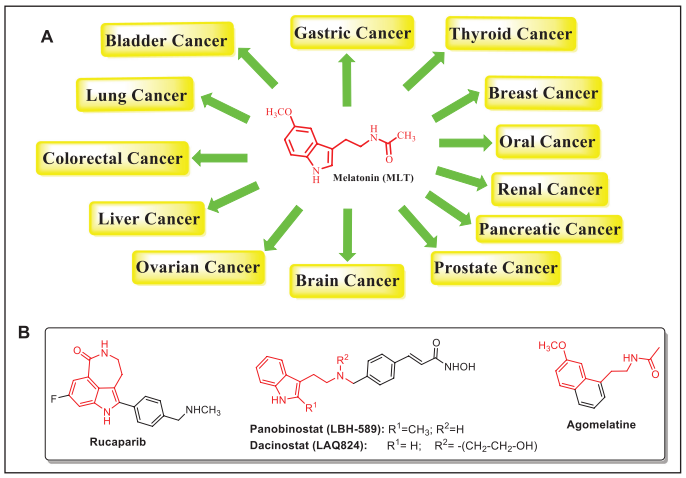

Figure 1. (A). *In vitro, in vivo*, and clinical action of MLT against various types of cancer. (B). Structures of selected clinically approved drug molecules incorporating an MLT portion.

Regarding the biological mechanism, the promising therapeutic potential of MLT for many types of malignancies *in vitro*, in animal models, and in cancer patients, have been closely associated via the direct and indirect modulation of recognized cell-intrinsic proapoptotic mechanisms implicated in cancer progression (Fig. 2) [8–10]. From an initial commentary in 2004 in which MLT could modulate cancer initiation and progression [11], the cytotoxic effects exerted by MLT have inspired the development of potential antineoplastic agents incorporating key features of MLT. In fact, various of them have been approved by the Food and Drug Administration (FDA) (Fig. 1B). Thus, for example, in 2020 Rucaparib (Rubraca®), a conformationally restrained MLT-analog was approved for the treatment of metastatic prostate cancer and recurrent ovarian carcinomas. Likewise, recently Dacinostat and Panobinostat were approved as chemotherapeutics agents in the treatment of prostate/breast cancer and multiple myeloma, respectively. Moreover, the naphthalenic bioisostere of MLT, Agomelatine, an FDA-approved antidepressant, has been also suggested recently as a new repurposed strategy for the treatment of colorectal cancer [12].

In addition to its anti-tumoral benefits, mounting evidence has indicated that MLT could be used as an adjuvant or protective anticancer drug in current chemotherapeutic regimes. In the first case, it was reported that MLT is able to synergize the chemotherapeutic effects of the anti-tumor drugs 5-FU or oxaliplatin in metastatic cancer [13–16]. Second, MLT has shown relevant protective benefits in clinical trials against the detrimental injuries of chemotherapy drug-induced toxicity in patients with cancer [17–21]. Moreover, convincing evidence

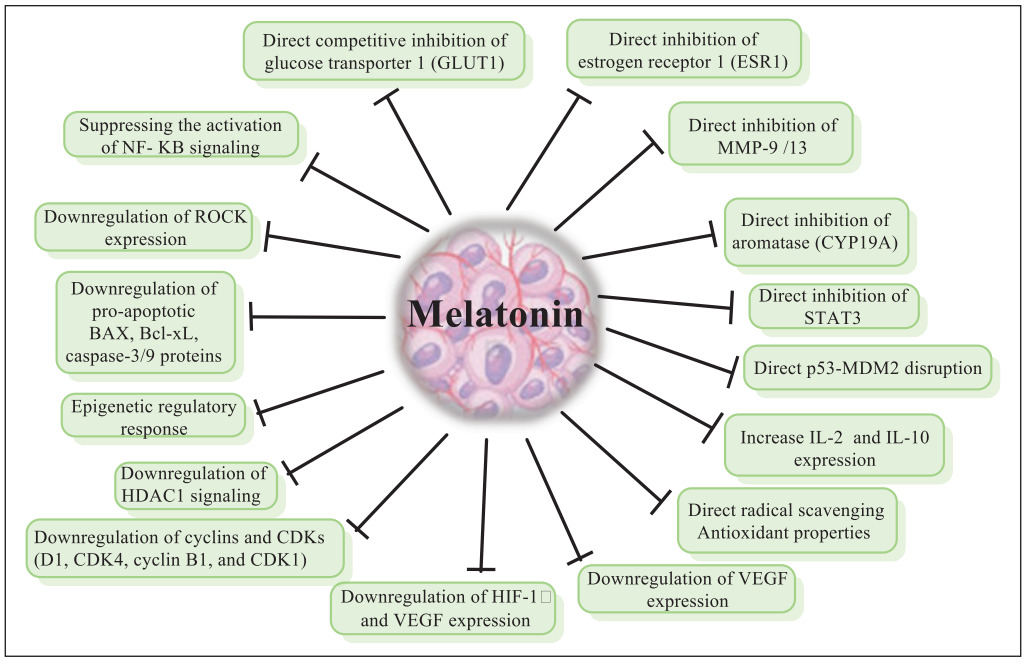

Figure 2. The most common pro-apoptotic mechanisms by which MLT mitigates cancer at the initiation, progression, and metastasis phases.

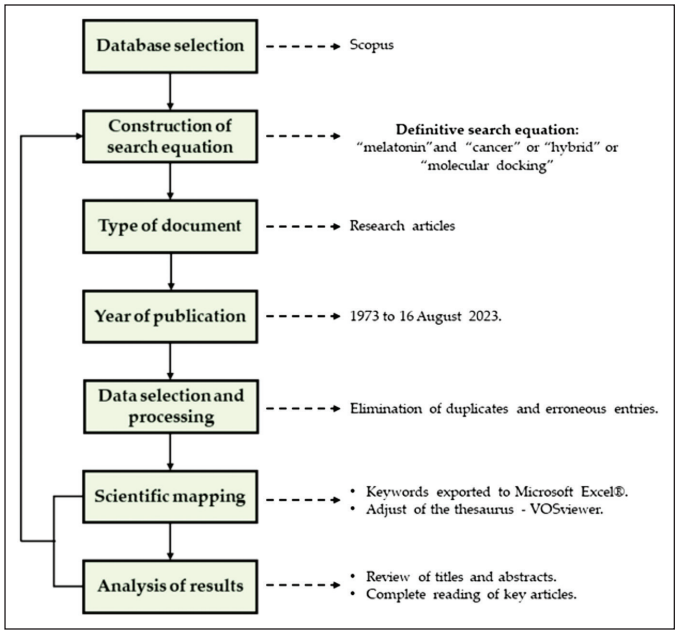

Figure 3. Methodological scheme for bibliometric analysis studies.

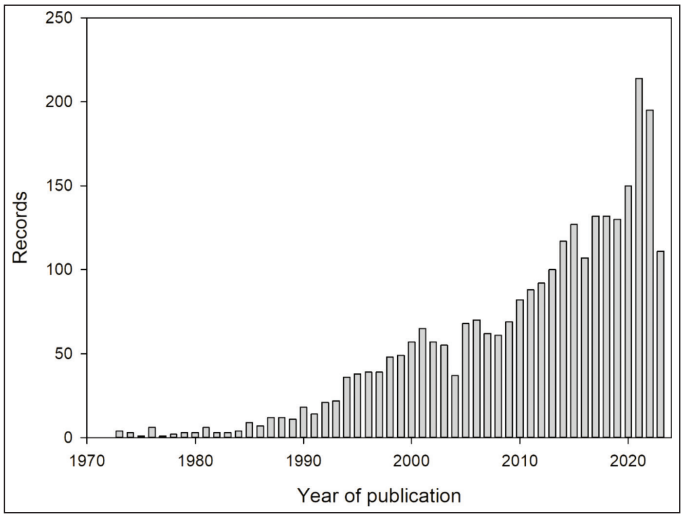

Figure 4. Evolution of published studies related to MLT, cancer, hybrid, and molecular docking from 1973 to 16 August 2023.

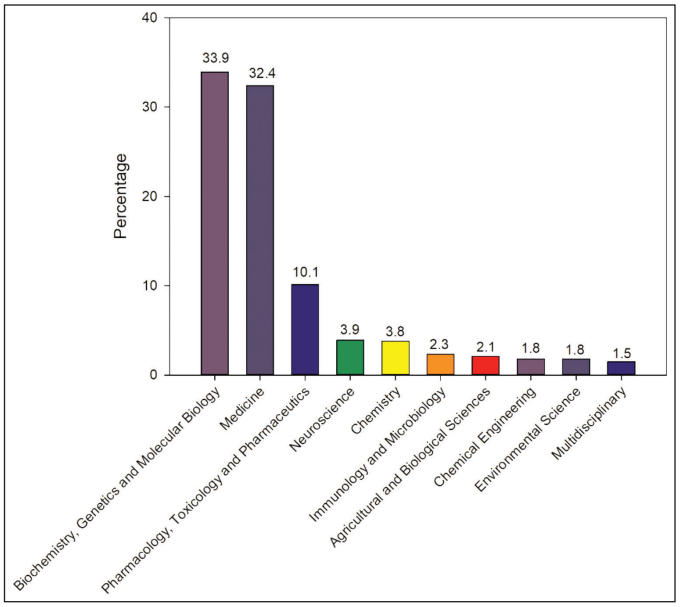

Figure 5. Top 10 areas of knowledge related to MLT, cancer, hybrid, and molecular docking from 1973 to 16 August 2023.

has shown that in cancer patients daily intake of oral MLT before bedtime improves the quality of sleep, and reduces the incidence of depressive symptoms [22–24]. Despite MLT being currently considered as a new and promising molecule that could be used in clinical oncological intervention, there are serious limitations due to its bioavailability, oral absorption, and rapid metabolism. When MLT was administered orally in normal healthy volunteers, it showed a poor absolute bioavailability of less than 3% while the intravenous MLT administration revealed serum values ranging between 9% and 33 % [25,26]. Recent research studying alternative routes for enhancing the pharmacokinetic response of MLT has been envisaged for cancer therapy, among them nanostructured lipid encapsulation [27], soft gel encapsulation [28], bioisosteric modifications on MLT structure, or through the design of large library of MLT-derivatives. In addition to these approaches, MLT also fulfills most of the requirements of a typical lead compound for rational drug design. In fact, from 1998 to nowadays, MLT has emerged as a promising structural prototype for developing hybrids and derivative molecules, particularly with anticancer benefits in both *in vitro* and *in vivo* models [29]. These efforts have led to a vast number of compounds containing an MLT portion, most of them have demonstrated to have not only potent antiproliferative and marked cytotoxic effects against the most common types of cancer, but are also more active than MLT. Findings, limitations, arguments, and comparison of derivatives and hybrids incorporating MLT will be pointed out in the discussion section.

MLT is synthesized in almost all living organisms including yeasts, bacteria, plants, and animals; however, the levels of MLT are significantly lower in nature. Due to this limitation and the current extensive pharmaceutical use and application of MLT in cancer, an economical large-scale production of MLT is necessary. Consequently, novel synthetic pathways have been proposed for the production of MLT via cheap and commercially available starting materials. Currently, simple synthetic methods have been devised for the preparation of MLT basically taking a compound containing an indole ring as synthon [30,31].

Taken altogether, MLT and its derivatives and hybrids showed high significance toward the development of new cancer drugs because of its diverse and potent oncolytic properties. A vast volume of information in the scientific literature suggests that MLT, its hybrids, and its derivatives are currently hotspots in many areas of research, mainly cancer. Because of that, a systematic approach that allows valuable insights into the quantitative aspects of scientific literature, including trends, emerging topics, and the evolution

Table 1. The top 10 most cited studies related to MLT, cancer, hybrid, and molecular docking from 1973 to 16 August 2023.

Title	Year	Journal	Citations[a]	Ref.
Oxidative stress: an essential factor in the pathogenesis of gastrointestinal mucosal diseases	2014	Physiological Reviews	1,386	[39]
Rotating night shifts and risk of breast cancer in women participating in the nurses' health study	2001	Journal of the National Cancer Institute	910	[40]
Molecular characterization of a second MLT receptor expressed in human retina and brain: the Mel(1b) MLT receptor.	1995	Proceedings of the National Academy of Sciences of the United States of America	843	[41]
MLT in edible plants identified by radioimmunoassay and by high-performance liquid chromatography-mass spectrometry	1995	Journal of Pineal Research	810	[42]
New hypotheses for the health-protective mechanisms of whole-grain cereals: what is beyond fibre?	2010	Nutrition Research Reviews	766	[43]
Night shift work, light at night, and risk of breast cancer	2001	Journal of the National Cancer Institute,	751	[44]
The basic physiology and pathophysiology of MLT	2005	Sleep Medicine Reviews	716	[45]
Night-shift work and risk of colorectal cancer in the Nurses' Health Study	2003	Journal of the National Cancer Institute	649	[46]
Effect of bright light and MLT on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial	2008	JAMA	639	[47]
MLT: a multitasking molecule	2010	Progress in Brain Research	532	[48]

[a]Data collected on 28th August 2023.

Table 2. The top five institutions publishing studies related to MLT, cancer, hybrid, and molecular docking from 1973 to 16 August 2023.

Institutions, city, and country	Number of publications
Azienda Ospedaliera San Gerardo Monza	103
University of Texas Health Science Center at San Antonio	87
Tulane University School of Medicine	49
Universidad de Cantabria	48
Harvard Medical School	44

Table 3. The top five journals publishing studies related to MLT, cancer, hybrid, and molecular docking from 1973 to 16 August 2023.

Journals (impact factor)	No. of publications
Journal Of Pineal Research (12.081)	265
Neuroendocrinology Letters (0.638)	49
International Journal Of Molecular Sciences (5.6)	38
Plos One (3.752)	34
Cancer Letters (9.756)	31

of research over time, is an alternative for presenting a general overview of MLT. Bibliometric analysis is a technique that helps to provide a macroscopic overview of large amounts of scientific literature, as is the case of MLT. This information can be used to assess the research patterns during a defined timespan. In the case of MLT, there are several reviews available, including studies as a promising anticancer drug lead [9,32]. Nevertheless, and to the best of our knowledge, a bibliometric analysis of MLT regarding cancer is still lacking. Therefore, the aim of this study is to carry out a bibliometric analysis of MLT and their derivatives and hybrids in cancer.

METHODS

Database selection and search strategy

This study has imported/collected data from the Scopus database (on 16 August 2023), which is one of the largest databases of peer-reviewed literature worldwide in the field of science and technology. The retrieved bibliographic data contains the most relevant studies related to both MLT and cancer as the main topics. The search equation was designed using the terms "melatonin," "cancer," "hybrid," and "molecular docking" and connecting them by using the Boolean operators "AND" and "OR": The final query was as follows:

Query: ((TITLE-ABS-KEY (melatonin) AND TITLE-ABS-KEY (cancer) OR TITLE-ABS-KEY (hybrid) OR TITLE-ABS-KEY ("molecular docking")) AND (LIMIT-TO (DOCTYPE,"ar"))).

Timespan: 1973 to 16 August 2023.

The search equation was queried within the fields of article title, abstract, and keywords, and further refined to only articles. Elimination of duplicate records was conducted by the medeley reference manager to address limitations or potential biases in the bibliometric analysis. See [33–37] for further details of the bibliometric analysis methodology. Figure 3 shows a scheme of the methodology applied during this study.

Data export and bibliometric indicators

The bibliographic data retrieved for the research articles were abstract, keywords, and both citation and bibliographical information. Data were downloaded from Scopus in CSV format and exported to Excel®. Subsequently, VOSviewer 1.6.19 was used for data analysis and visualization [38]. In addition, bibliometric indicators such as the volume and growth of issued articles, subject areas, co-occurrence keywords network visualization, co-occurrence keywords overlay visualization, leading institutions and journals (and their

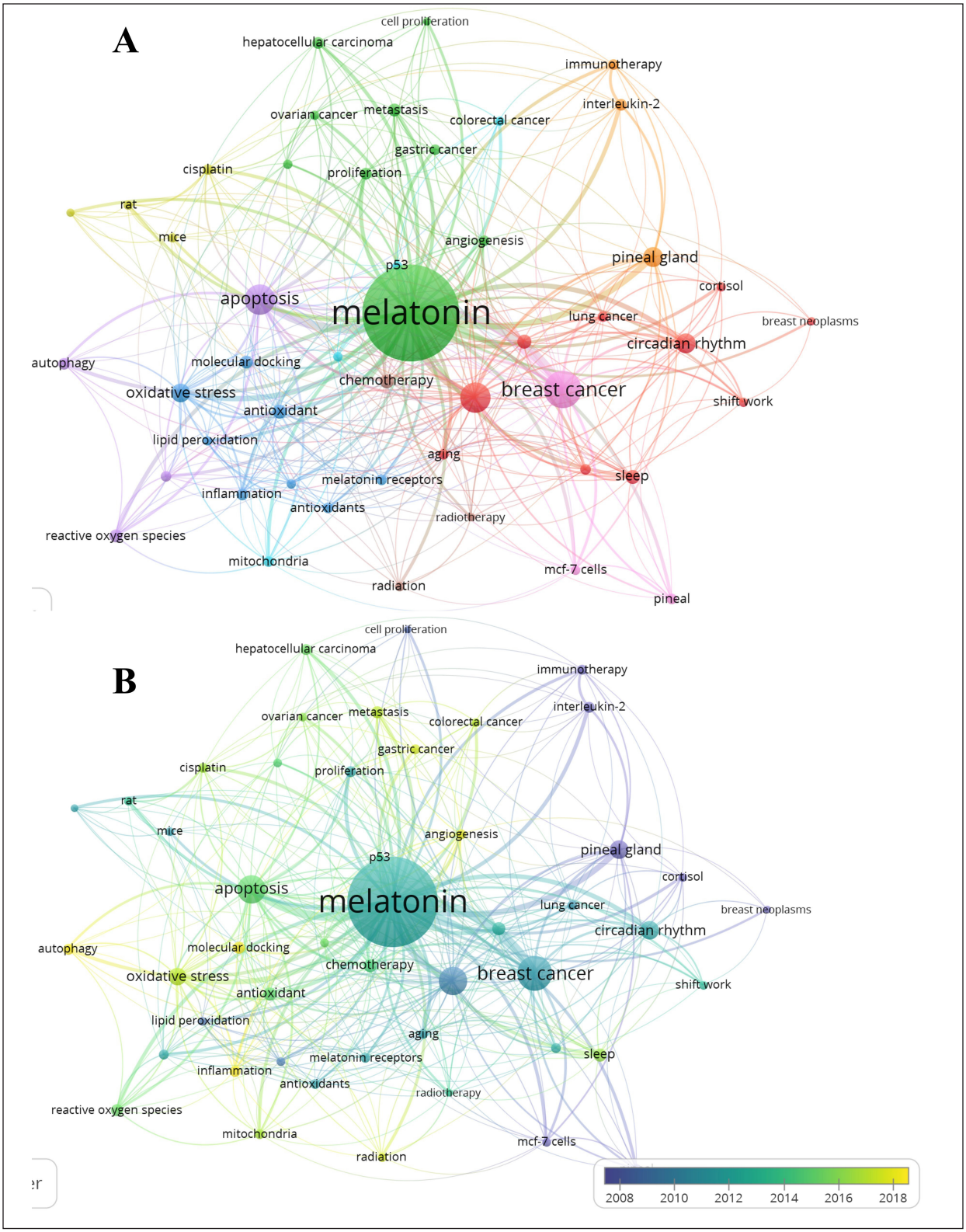

Figure 6. Bibliometric network of studies related to MLT, cancer, hybrid, and molecular docking from 1973 to 16 August 2023. A) Research-topic map. B) Research-topic map with time overlap. The nodes represent the author´s keywords while the size of the circle indicates their occurrences (i.e., the number of publications that have the corresponding term in their title or abstract). In addition, the width of the line linking them is proportional to the strength of the relationship between the author´s keywords, and the distance between them indicates the relatedness of the nodes. Note: minimum number of occurrences of a keyword is 18.

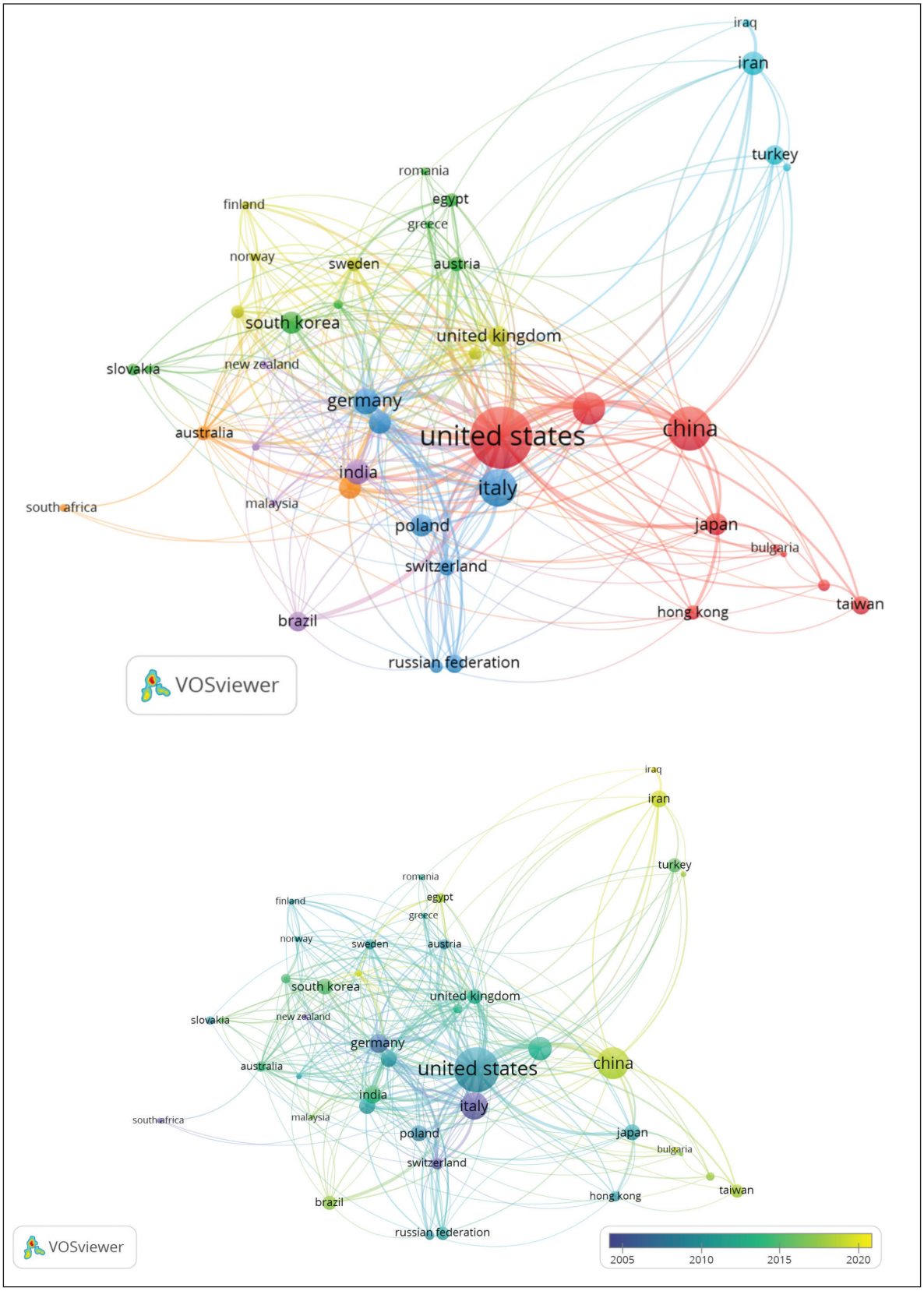

Figure 7. Bibliometric map of global collaboration network among countries researching on MLT, cancer, hybrid, and molecular docking from 1973 to 16 August 2023. A) Global collaboration network among countries. B) Global collaboration network among countries with time overlap. The nodes represent the countries while the size of the circle denotes the number of publications. In addition, the width of the line linking them is proportional to the strength of the relationship between countries, and the distance between them indicates the relatedness of the nodes. The minimum number of documents in a country is 10.

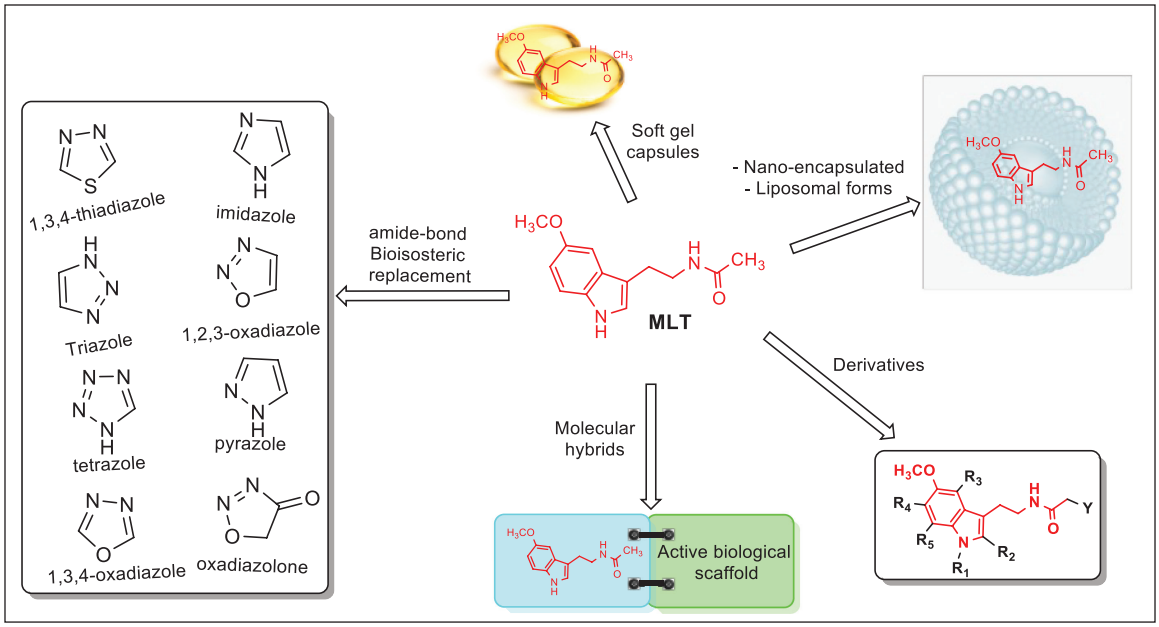

Figure 8. Different approaches for improving MLT pharmacokinetics properties: molecular hybridization, structure modification (derivatives), bioisosterism, nanotechnology, and softgel capsules.

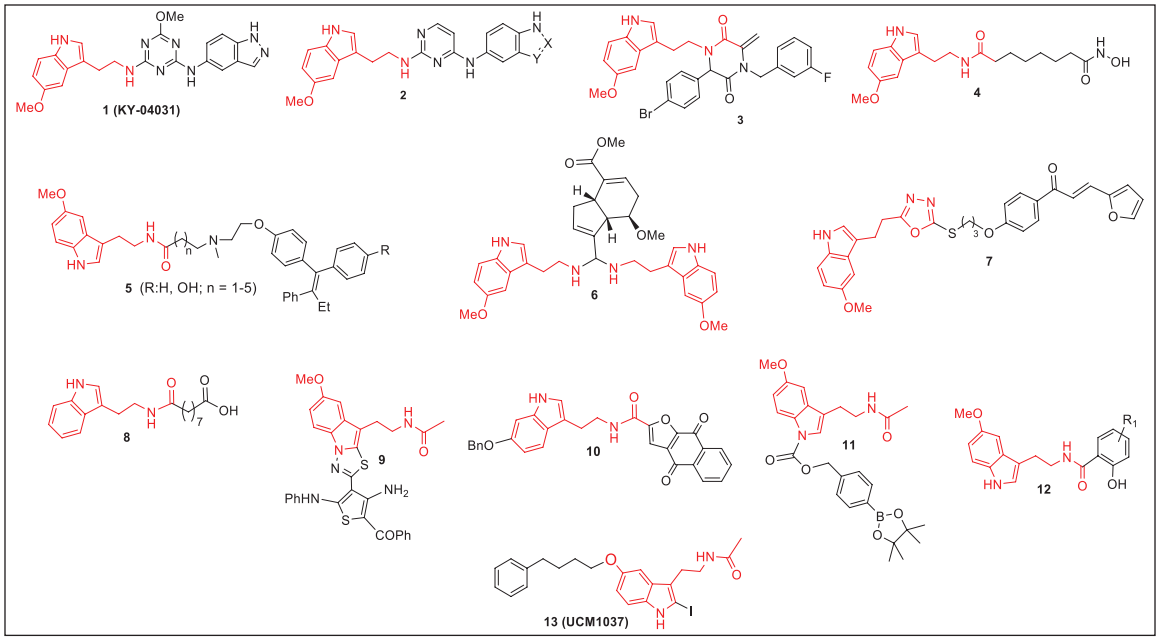

Figure 9. Molecular structures of highly potent derivatives and hybrid molecules incorporating MLT as emerging drugs for cancer intervention.

impact factors), the top 10 most cited studies, and collaboration networks among the countries, were evaluated.

RESULTS

Evolution of publishing papers related to MLT

A total of 2,792 articles were retrieved from the scopus database. Figure 4 shows the growth of published studies related to MLT, cancer, hybrid, and molecular docking from 1973 to 16 August 2023. During this period, an increase in the number of articles issued was observed since 2004. Besides, the main areas of knowledge of those studies were: (i) *Biochemistry*, *Genetics,* and *Molecular Biology,* (ii) *Medicine, and* (iii) *Pharmacology*, *Toxicology,* and *Pharmaceutics*, with 33.9%, 32.4% and 10.1% of the records, respectively (Fig. 5). Furthermore, the United States and China ranked first and second, respectively, followed by Italy, Spain, and Germany as the leading countries in the numbers of published articles in this field.

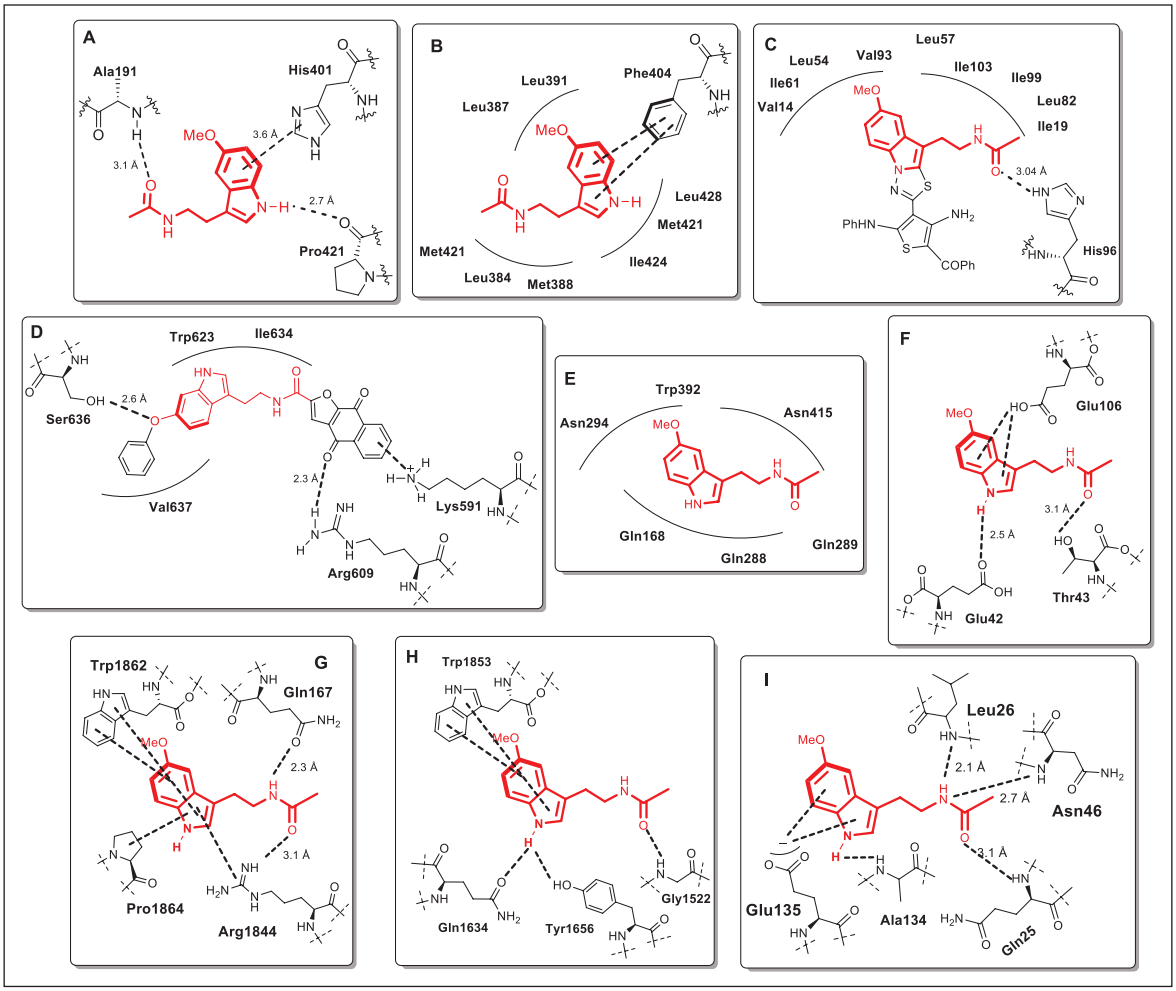

Figure 10. 2D-ligand interaction plots after docking studies for MLT, its hybrids, and its derivatives within the active site of five critical target-proteins associated with the initiation and progression of tumors. A) Binding of MLT with MMP-9. B) Binding of MLT with ESR1. C) Binding of MLT with MDM2. D) Binding of MLT with STAT3. E) Binding of MLT with GLUT1. F) Binding of MLT with Ile6. G) Binding of MLT with TP53. H) Binding of MLT with mTOR. I) Binding of MLT with TNF-α.

Journals, institutions, and publications with the highest impact

Table 1 shows the top 10 cited studies related to m MLT elatonin, cancer, hybrid, and molecular docking, while Table 2 displays the top five leading institutions in this field. Here, and as expected, the leading institutions are in the top countries previously mentioned (Italy, the United States, and Spain). Furthermore, Table 3 shows the leading journals that issued the articles on this topic, and their impact factor.

Bibliometric networks of MLT, cancer, hybrid, and molecular docking

The co-occurrence of the author's keywords network contains nine clusters and 48 nodes (Fig. 6A). Among them, ovarian cancer, gastric cancer, colorectal cancer (green and light blue clusters), breast cancer (pink cluster), lung cancer (red cluster), chemotherapy (brown cluster), inflammation, and molecular docking studies (blue clusters) are highlighted. In addition, Figure 6B shows the topics on which the researchers centered their studies between 2008 and 2018. It is noticeable that in 2018 the studies concentrated on molecular docking and inflammation (see yellow nodes in Fig. 6B). Thus, this could indicate that they are emerging topics in this field. Furthermore, Figure 7 shows the countries' collaboration networks. Clearly, the United States, China, Italy, Spain, and Germany displayed the biggest nodes in this network. Figure 7B shows a research-topic map with time overlap. Here, China, Iran, Iraq, Saudi Arabia, and Egypt are the leading countries between 2018 and 2020. Based on the described results, and thanks to bibliometric indicators, the discussion of this study was concentrated on molecular docking studies of MLT and their anticancer activities against several types of cancer.

DISCUSSION

Pharmacokinetic limitations of MLT inspired its hybrids and its derivatives

Undoubtedly, credible evidence has proven that MLT possesses a range of beneficial effects against cancer. Nevertheless, MLT exhibits a serious pharmacokinetic

limitation mainly because of its poor oral bioavailability and short half-life, as a result of its rapid metabolic inactivation, thereby restraining its therapeutic use [49]. There is conflicting evidence on the pre- and clinical efficacy of exogenous MLT. The pharmacokinetic properties of MLT have been extensively studied in critically ill patients, evidencing that following oral and intravenous administration, the bioavailable amount of MLT was generally low ranging from 3% to 33% critically affecting the drug response critically [50,51]. In line with this, many strategies have been rationalized to facilitate selective applications in medicine and improve the pharmacokinetic properties of MLT (Fig. 8). Interestingly, these novel approaches have successfully prolonged the release, efficacy, and safety of MLT. In this regard, first, the acetamido group of MLT has been bioisosterically replaced by classical amide bond bioisosteres units such as 1,2,3-triazole, 1,n,ω-oxadiazole, oxadiazolone, 1,3,4-thiadiazole, imidazole, tetrazole, and pyrazole [52–54]. In addition to their classical bioisosteres, the pharmacokinetics of alternative administration routes such as nano encapsulated, liposomal forms, and soft gel capsules of MLT are now emerging exhibiting superior effectiveness in many pathological processes [28,55,56,27,57]. Finally, another point of special interest in this bibliometric analysis is the structure of MLT has been used in medicinal chemistry as a pharmacophoric motif for the design of new potential derivatives and hybrid compounds for anticancer intervention which have shown to possess potent *in vitro* and *in vivo* anti-tumoral effects in a variety of malignancies [58,59]. In this scenario, numerous investigations, reports, and articles have demonstrated that the incorporation of an MLT portion in diverse active cores increases the effectiveness (Fig. 9). These efforts have highlighted MLT-triazino, -pyrimido, and -piperazine-2,5-dione conjugates, **1** (KY-0403), **2**, and **3**, respectively, with potent cytotoxic responses against prostate, lung, colon, breast, and pancreatic cancer cells [60–62]. A recent investigation in MCF-7, PC-3M-Luc, and HL-60 cancer cell lines treated with the MLT–vorinostat hybrid **4** showed strong oncostatic action which is driven by the histone deacetylase (HDAC) inhibition [63]. MLT was also linked to the antitumoral FDA-approved Tamoxifen given hybrids **5**, which exhibited potent anticancer activity (2.2 nM–3.0 pM) in a mouse model [64]. Furthermore, its ability to alter tumor cell metabolism was evidenced when MLT was combined with the anticancer natural occurrent monoterpenoid Genipin to afford the hybrid ligands **6**, which exhibited potent cytotoxic activities through induction of apoptosis and arrested the cell cycle in five cancer cell lines (SW-480, A-549, HL-60, SMMC-7721, and MCF-7) with IC_{50} ranging from 0.90 μM to 0.43 μM [65]. More recently, it was reported that a series of hybrids containing the oxadiazole-bioisostere MLT and chalcones showed a potent antiproliferative effect against SW480 human colon cancer cell, highlighting the compound **7**, which displayed an IC_{50} value very close to 260 nM [53]. In this same line, it was reported that the MLT-derivative **8** was very potent against the human colorectal adenocarcinoma HT29 cell line revealing an IC_{50} = 6 nM [66]. In 2021, novel MLT derivatives were also reported, particularly compound **9**, which possesses valuable cytotoxic effects against two human cancer cell lines, breast cancer (MCF7) and colon cancer (HCT-116) with an IC_{50} value ranging from 11 to 37 μM [59]. Taking advantage of the oncostatic benefits of MLT, recently the Zhang Group and collaborators reported a new series of hybrids incorporating in the core structure of MLT a portion of napabucasin, an FDA-approved drug for treating patients with metastatic colorectal cancer. Of those hybrids, compound **10** showed greater growth inhibitory effects against different tumor cells (HepG2, MDA-MB-231, and A549) than napabucasin, with IC_{50} values of 1.06, 1.38, and 1.3 μM, respectively [67]. Furthermore, it was reported that hybrids of MLT containing ROS-responsive arylboronate **11** portions exhibited strong toxic effects in cervical cancer cells (HeLa) [68]. Potential anticancer benefits of MLT-salicylic acid hybrids **12** were also investigated against a human gastric carcinoma MGC-803 cell line, showing marked antiproliferative and cytotoxic activity with IC_{50} in the range of 43 to 62 μM [69]. The antiproliferative and pro-apoptotic activity of MLT analogs was also demonstrated against melanoma and breast cancer in both *in vitro* and *in vivo* models, that, particularly compound named UCM 1037 (**13**) induced apoptosis on human breast cancer cell line (MCF-7), and caused suppression of tumor growth in a mice model [70].

Biochemical mechanism of MLT, its hybrids, and derivatives: highlights and computational studies

As mentioned above, MLT, its hybrids, and its derivatives provide a new direction in the development of new antineoplastic agents. Recent experimental evidence has revealed that this valuable proapoptotic action of MLT as well as of these MLT-based compounds on tumor cells could be strongly related to targeting specific receptors mainly involved in cancer cell proliferation and survival (Fig. 2). Therefore, including MLT, numerous investigations have unequivocally demonstrated that these molecules are capable of modulate at least 19 proapoptotic mechanisms, thus, 1) by acting as a free radical scavengers and antioxidant at the mitochondrial level [71,72]; 2) by helping to regulate the immune system [73] activating the T cells by increasing the secretion of interleukin-2, interleukin-10 [73,74]; 3) in affecting DNA damage response by interacting with the direct mediators of cell cycle arrest, apoptosis and autophagy [75–77]; 4) by downregulating the amounts of vascular endothelial growth factor (VEGF) [78]; 5) disrupting the p53/MDM2 complex formation by inhibiting the phosphorylation of MDM2 [59,79,]; 6) inhibiting the progression of gastric cancer by direct binding to the estrogen receptor 1 (ESR1) [80]; 7) in suppressing lung adenocarcinoma cells growth by targeting HDAC1 signaling [81]; 8) by inhibiting directly the activation of the signal transducer and activator of transcription 3 (STAT3) in metastatic colorectal cancer, pancreatic cancer, non-small cell lung cancer, and gastric cancer [67]; 9) on human prostate cancer, promoting cell death through a competitive inhibition for the binding sites into the glucose transporter 1 (GLUT1) [82,83]; 10) by enhancing the BAX expression, reducing Bcl-xL production and activating caspase-3 and caspase-9 [84]; 11) by suppressing the activation of the nuclear factor κB (NF-κB) signaling [85]; 12) in decreasing breast cancer metastasis by modulation of Rho-associated kinase protein-1 expression [86]; 13) by suppressing the MMP-13 expression

in metastatic prostate cancer cells [87]; 14) by interfering with MMP-9 activity through a direct docking into the active site of MMP-9 [88]; 15) in reducing the expression of cyclins and CDKs (D1, CDK4, cyclin B1, and CDK1) in human osteosarcoma cells [89]; 16) by inhibiting breast cancer cell lines through a suppressive role on aromatase activity [90,91]; 17) by exerting a potent and sustained anti-angiogenic action by inhibiting HIF-1α and VEGF expression [10, 92–95]; 18) by regulating the epigenetic response in altering the status of DNA methylation in different cancer cells and models, which is nowadays a potent and effective strategy for treatment of cancer patients [96]; and 19) in preventing survival of neoplastic cells mimicking the role of sexual hormones on hormonal receptors, particularly in the cell proliferation of prostate, breast, and ovarian cancer cells [97–100].

More specifically, activation of these above-mentioned pro-apoptotic mechanisms by MLT occurs through ligand binding to specific receptors. Various studies that included enzymatic and molecular docking protocols have been carried out to understand at the molecular level the anti-tumoral role of MLT. The first of these results revealed that MLT is able to interfere with the matrix metallopeptidase 9 (MMP-9) activity by interacting with key residues within the catalytic site of MMP-9 (Fig. 10A) affecting the catalytic contribution of the histidine-coordinated zinc-binding site, as well as two surrounded crucial amino acid residues (Pro421 and Ala191) [88]. MMP-9 is a proteolytic enzyme that is implicated in diverse roles in the growth and proliferation of malignant cells in the host organ. Second, based on molecular docking, it was also evidenced that MLT could inhibit the progression of gastric cancer by blocking the ESR1 with a binding affinity of 7.1 kcal/mol making key contacts with those crucial catalytic residues in the ESR1-active site (Fig. 10B). Currently, ESR1 is a crucial target to fight gastric cancer [80]. Third, in breast cancer, another computational study has evidenced that anticancer activity of MLT and MLT-based derivatives would be closely related to inhibition of the MDM2, by interacting with those crucial residues in the p53-binding pocket of MDM2 in a manner sufficient to disrupt the MDM2 and p53 interaction and enhance the functions of p53 (Fig. 10C) [59,79]. Blocking the MDM2–p53 interaction has become a new direction to combat different human cancers.

Fourth, recent studies have also evidenced that MLT-derived possess a repressive effect on the coding function of the STAT3 protein, by binding into the STAT3-SH2 domain through two hydrogen bonds with key Ser636 and Arg609 residues, one cation-π contact (with Lys591 residue), and several hydrophobic interactions (Fig. 10D). Targeting STAT3 activity has emerged as a rationale drug target to combat tumor progression in most human cancers involving organs such as the pancreas, brain, breast, ovaries, and prostate, among others [101]. Fifth, to confirm the potential mechanism by which MLT represses the growth of human prostate cancer cells, *in vitro*, enzymatic followed by molecular docking studies also evidenced that MLT is able to reduce the uptake of glucose by blocking the glucose-binding site into the GLUT1 receptor making key interactions with those amino acids residues (Fig. 10E) crucial for facilitating glucose transportation (Gln168, Gln288, Gln289, Asn294, Trp392, and Asn415) [83]. In prostate cancer, GLUT1 is overexpressed, then compounds acting as competitive inhibitors for the glucose-binding site of GLUT1 could become promising drug candidates to be used in prostate cancer intervention [102]. Finally, target analysis and molecular mechanism studies suggested that MLT would mitigate cancer by directly binding to at least four other proapoptotic target proteins, as reported recently by Suriagandhi and collaborators [103]. Thus, MLT would interact with good binding affinity to IL-6 (Fig. 10F), TP53 (Fig. 10G), mTOR (Fig. 10H), and TNF-α (Fig. 10I) receptors, which are overexpressed in many types of cancer cells and play a critical role in promoting tumor initiation and progression.

FUTURE PERSPECTIVES

Global collaboration

Given the interdisciplinary nature of cancer research and its impact on society, future endeavors may involve increased collaboration between countries, researchers, clinicians, and industry partners on a global scale. Open sharing of data could accelerate progress in the field. In addition, data science could play a crucial role in advancing the studies of MLT. Data integration and mining (omics data integration), bioinformatics analysis (pharmacogenomics), and machine learning for prediction could be useful.

Development of novel derivatives and hybrids

Future research may involve the design and synthesis of novel MLT derivatives and hybrids with enhanced bioavailability, stability, and targeted delivery properties. This could eventually improve the pharmacokinetics and therapeutic potential of MLT -based anti-cancer agents.

Preclinical and clinical trials

As promising preclinical results accumulate, more emphasis may be placed on conducting rigorous clinical trials to assess the safety and efficacy of MLT derivatives and hybrids in diverse cancer populations.

CONCLUSION

From an initial commentary in 2004 in which MLT could modulate cancer initiation and progression, it has seen how MLT its hybrids, and its derivatives have gained special interest in the scientific community. Our bibliometric analysis revealed that:

i) A total of 2792 articles related to MLT and MLT-derived compounds have been reported exhibiting valuables anticancer properties issued in journals indexed in the Scopus database from 1973 to 16 August 2023.

ii) A clear rise in the number of articles publishing MLT in cancer was observed from an initial commentary in 2004.

iii) The main areas of knowledge of those records were: Biochemistry, genetics and molecular biology, medicine

and pharmacology, toxicology, and pharmaceutics, while the United States, China, Italy, Spain, and Germany are the leading countries in the numbers of published articles.

iv) It was found that MLT and MLT-derived compounds possess potent responses against at least 13 cancer cell lines (gastric, thyroid, breast, oral, renal, pancreatic, prostate, brain, ovarian, liver, colorectal, lung, and bladder cancers) in both *in vitro* and *in vivo* models.

v) Current advances in molecular, biochemical, and computational analysis have documented that the antitumoral benefits provided for MLT, its hybrids, and derivatives not only is caused by their well-known antioxidant properties but it also has been well-documented that these compounds are able to modulate o to interfere with at least 19 proapoptotic signaling pathways.

vi) Three compounds incorporating an MLT moiety have recently received approval by the FDA as chemotherapeutics for clinical use in metastatic prostate cancer, breast cancer, and multiple myeloma treatments.

vii) Regarding MLT and MLT-derived compounds, the present network analysis also revealed that apoptosis, chemotherapy, breast cancer, gastric cancer, colorectal cancer, prostate cancer, and molecular docking studies are emerging topics in this field.

From these bibliometric findings, undoubtedly MLT, its derivatives and hybrids possess great potential to be considered in new avenues toward cancer research and treatment. More importantly, bibliometric results covering the scenario of MLT, derivatives, and hybrids in cancer, play a significant role in identifying the value of these scaffolds in future research directions aimed at developing new anti-cancer drug candidates.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVAL

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

PUBLISHER'S NOTE

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INFORMED CONSENT

For this type of study, formal consent is not required.

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