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# THERAPEUTIC APPLICATIONS OF GALLIUM COMPOUNDS

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**Abstract:**

***Background:*** *Classified as a Group IIIA metal, gallium, as well as its compounds, has been presenting several therapeutic activities in the last decades. Gallium compounds garnered considerable attention mainly due to their ability to mimic iron, presenting antimicrobial activities and showing antiproliferative and antimitotic activity against some cancers.*

***Method:*** *This review article provides a survey of the main therapeutic applications and analysis of the characteristics of in vivo and in vitro preclinical trials with gallium and its respective compounds.*

***Results:*** *Given the therapeutic potential of gallium, its compounds are promising at various stages of preclinical studies for promoting therapeutic action. In this work we discussed about Gallium antimicrobial and antineoplasic activities, its effects in bone metabolism and hypercalcemia, as well as immunosuppressive, anti-inflammatory and antimalarial properties.*

***Conclusion:*** *Gallium and its complexes show promising pharmacological options for various diseases, representing a major breakthrough in therapy as they have potential for new drug candidates. However, more studies are still necessary.*

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## INTRODUCTION:

Belonging to group IIIA, gallium is a metal used in various applications due to its therapeutic properties [1]. In 1931, gallium was identified as a potential therapeutic agent due to reports of syphilis eradication in rabbits and *Trypanosoma evansi* in mice. Later, gallium ($^{67}$Ga) was identified as a potential imaging agent for tumor diagnosis [2,3]. Among the various therapeutic applications of gallium, studies have highlighted the anticancer and antibacterial activities [4].

Gallium nitrate is considered the first gallium compound that has exhibited anticancer properties in humans [1,5,6], affecting several types of cancer, even in cancers that did not have therapeutic responses with conventional chemotherapy. One strategy that can intensify cancer treatments is by combining gallium compounds with conventional therapies, but follow-up is needed to avoid triggering side effects [7,8,9,].

Excessive consumption of antibiotics can promote the development of bacterial resistance to these drugs. Another gallium-enhancing therapeutic alternative is to bypass classic antibiotics, as inorganic antimicrobials have several advantages, allowing them to reach a broad spectrum of bacteria and they are less vulnerable to develop resistance mechanisms. Gallium and its compounds are metallic antimicrobials, in which activity against several bacteria has been confirmed [10,11,12].

Since gallium has the property of mimicking and competing with iron in biological processes, when absorbed, cells suffer a disruption in their respiratory capacity, since unlike iron, gallium does not undergo reduction reactions intracellularly. Thus, gallium blocks the proliferation of pathological cells, especially cancer and bacterial cells [7,13,14,15,16].

This review article provides a survey of the main therapeutic applications of gallium and its respective compounds, analyzing their potential in preclinical (*in vitro* and *in vivo*) trials.

## THERAPEUTIC APPLICATION OF GALLIUM COMPOUNDS:

Gallium is not part of human physiology; however, this metal has the ability to share chemical properties, resulting in the interference of some physiological processes. Several *in vivo* and *in vitro* preclinical studies have been investigated to show the ability of gallium and its compounds to evaluate their potential therapeutic effects. Where gallium compounds present themselves as potential metallic drugs.

**Antimicrobial agents in the biological system:**

Antimicrobial classes differ according to their physical, chemical, and pharmacological properties, and their mechanisms of action. Despite all the efforts from the pharmaceutical industry to research and produce new and more effective antimicrobial drugs, indiscriminate use and inappropriate prescriptions are one of the key factors in developing bacterial resistance [17,18,19].

The antimicrobial nature provided by metals was argued by the Swiss chemist Nägeli, where the author idealized the “oligodynamic effect”, which is a toxic characteristic effect found at very low concentrations. Due to their ability to have anti-infectious effects, metallic compounds have been showing great interest directed to clinical applications [20].

Bacterial resistance is a progressive problem, and since this problem is distributed worldwide, the development of pharmacological alternatives is of great relevance. Unlike classic antibiotics that have a specific action process, metals and metal compounds are capable of reaching groups of various biomolecules, making it less prone to develop resistance [21].

Due to the need in the development of new drugs capable of fighting multiresistant bacteria and the lack of new pharmaceutical antibiotics, gallium ($Ga^{3+}$) has been showing promising antibacterial activities due to its pharmacological properties in mimicking iron [22,23,24]. When $Ga^{3+}$ is supplied to living cells, it has the ability to replace Iron ($Fe^{3+}$), as the major carriers of iron (transferrin and lactoferrin) cannot distinguish these metals, carrying $Ga^{3+}$ to the bloodstream and plasma in the form of complexes with these proteins [25]. Due to this fact, $Ga^{3+}$ is considered a “Trojan Horse” as it disrupts $Fe^{3+}$ dependent bacterial metabolism processes [11,21,26,27].

Since gallium binds to siderophores, which are molecules that are part of the bacterial iron absorption system, it is believed that bacteria are capable of sequestering gallium through their iron absorption systems. Unlike $Fe^{3+}$, $Ga^{3+}$ cannot be reduced, and due to this fact, several bacteriological processes are blocked, where the change between reduced and oxidized iron would occur. Referring to its potential antibacterial activity, gallium has been shown to be absorbed by Gram-positive and Gram-negative bacteria [21,24,28,29].

Several iron-containing enzymes are related to the critical functions of bacteria, such as metabolism, respiration, DNA synthesis and repair, and response to oxidative stress. Since gallium has similarities to iron, it promotes multiple deleterious effects on bacterial cells. A large proportion of pathogenic bacteria require iron and when there is an increase in the availability of this chemical compound in the host, the extension of the disease may be exacerbated [20,30,31,32].

According to the World Health Organization, there is a predominance of burns among developing and underdeveloped nations. As the physiology of the burn removes or impairs the natural integrity of the skin due to thermal injury, 75% of those affected die from the onset of systemic infection. Among the most prevalent pathogens that infect burn wounds, *P. aeruginosa* is the most prevalent, causing rapid proliferation [31].

In clinical settings, there is a huge concern that *P. aeruginosa* has increasing resistance to antibiotics, including cephalosporins and imipenem, which are considered the "gold standard" treatments. Due to this fact, the development of new drugs is extremely important Gallium maltolate (GaM) was found to be effective in preventing early proliferation and reduced mortality after *P. aeruginosas* colonized the burn-affected region [31].

A study by Kaneko et al. addressed the antimicrobial activity of gallium through in vitro studies. At low concentrations gallium was able to inhibit growth of P. aeruginosas as well as prevented biofilm formation, suggesting therapeutic efficacy due to interruption of iron metabolism [33].

Studies show the antibacterial properties of curcumin associated with gallium ions in order to enhance its effect. Jahangoshaei et al. produced gallium curcumin and gallium dicetylcurcumin and evaluated their interference with the peroxidase enzyme, which is one of the enzymes used by pathogenic bacteria. In addition, the action of these complexes on tumor cells was also evaluated. As a result, the complexes showed a greater therapeutic action in tumor cells when compared to enzymatic inhibition [34].

Lessa et al. presented a review of gallium complexes and it was identified that in relation to antimicrobial activities there is some evidence that gallium is effective against experimental syphilis in rabbits [35]. As well as other studies have also identified efficacy against trypanosomiasis [36] and tuberculosis [37].

A study by Gao et al. [38] proposed a new strategy to intervene in bone implant-related infections through the formation of Magnesium metal alloys with gallium and strontium ions (Ga and Sr 0.1% by weight). Ga and Sr-containing alloys were found to have *in vitro* antibacterial activity against for *S. aureus*, *S. epidermidis* and *E. coli* demonstrating that Ga played a key role against the viability of all selected bacterial strains. The literature also reports that when there is gallium incorporation in titanium implants, a superior bacterial inhibition against *Acinetobacter baumannii* is promoted [39].

Xu et al. developed a three-dimensional antimicrobial artificial structure based on collagen and gallium nitrate, and evaluated antimicrobial activity, cytotoxicity and biocompatibility. According to the antimicrobial (against *S. aureus* and *P. aeruginosa*) and cytotoxicity tests, the structure containing the 0.025% gallium was the most promising. Featuring adequate pore size as well as high porosity and enzymatic degradation, a high release rate of $Ga^{3+}$ was observed in the first 24 hours, as well as a significant cytotoxicity when the mass fraction was higher than 0.05%, that is, the relative growth rate increased with decreasing fractions of mass. Thus, this artificial dermal structure can block wound and implant infection and promote cell proliferation [12].

Qiao et al. synthesized functional gallium Polidopamine-$SrTiO_3$ nanotubes. Gallium in this coating was able to prevent infections, having bacteriostatic and bactericidal functions, and not developing bacterial resistance. Sr showed an osteoinductive effect, stimulating bone formation. The synergistic action of Ga and Sr resulted in an increased cell proliferation [40].

**Antineoplastic activity:**

Gallium is a chemical element of the boron family and has an oxidation number that can be +1 or +3, the latter being the most present in its compounds such as oxide and salts. This property of this element is important as it allows to elucidate some antimicrobial and antitumor actions [41]. Initial studies regarding antitumor action of gallium were described by Smith et al. [42] who observed an ability of this chemical element to bind to cancer cells in bladder cancer patients, raising questions and perspectives on the use of gallium as a therapeutic agent.

Because gallium has in most of its chemical bonds the oxidation number +3, some researchers have suggested the mechanism of action for $Ga^{3+}$ cation, justifying bactericidal and anticancer therapeutic

actions due to the absence of the ability of $Ga^{3+}$ to reduce when present in the biological systems [43,44].

Cells generally have a superficial transferrin receptor [45]. Gatter et al. described that cancer cells (lymphomas, bladder, breast and urethra) have an increase not only in the number of transferrin-cation complex receptors, but also increase the endocytosis rate of this complex. Thus, if the ferric ions were replaced by the gallic ions, the neoplastic cells would not be able to reduce the cation to the 2+ charge and thus would not be able to promote their internal biochemical processes [46].

From this perspective, there is a therapeutic action with the use of gallium salts, but there are some disadvantages, as iron deprivation in the body can generate some physiological changes such as anemia, increased levels of zinc and porphyrin, since part of the serum transferrin would carry much more gallic ions in detriment of ferric ions. This was a case observed in cancer patients from an *in vivo* study using gallium nitrate [47].

One of the physiological actions that is also altered by replacing $Fe^{3+}$ for $Ga^{3+}$ is deoxyribonucleic acid (DNA) synthesis in target cells. This is because DNA synthesis requires an enzyme called ribonucleotide reductase, where its R2 region is dependent on iron cations [48,49]. Thus, it can be said that there is a high probability of inhibition of cellular metabolism, regardless of their nature (healthy or carcinogenic) generated by gallium-based compounds when they replace ferric compounds. In addition to these studies, cases of proteasome inhibition in multiple myeloma and some lymphomas have been reported, according to O'Connor et al. [50].

Chitambar [51] describes a series of gallium compounds that have been studied for therapeutic use against cancer. Among them, there is gallium nitrate, which was considered the pioneer in the studies. Generally, phase II studies were performed in which patients with prostate, breast, bladder, non-Hodgkin's lymphoma and Hodgkin's lymphoma cancers underwent gallium nitrate treatment. The antineoplastic action of gallium nitrate in bladder cancer and non-Hodgking lymphoma was considered promising. Later on, gallium was associated with antineoplastic agents used in the clinic, such as vinblastine and hydroxyurea, obtaining satisfactory results [52].

Researchers have identified that gallium nitrate was reducing serum calcium levels, and due to this observation, more studies have been conducted. It was identified that bone resorption of calcium was being decreased, so that gallium nitrate may be used as a calcium reducing agent in malignant hypocalcemia [53]. Although the Food and Drug Administration (FDA) has approved the injectable pharmaceutical form of gallium nitrate for clinical use, gallium nitrate has been studied in tablet form, yielding promising results [26].

Gallium chloride is also a substance that inhibits malignant cell growth and has a similar therapeutic action to gallium nitrate [26]. Research groups performed tests of parenteral and oral gallium chloride in mice and it was observed the reduction of mammary adenocarcinomas, but it was identified that the bioavailability of the oral form of gallium chloride was low, requiring adjustments [54].

Salem et al. obtained betaine-associated gallium tetrachloride, and also obtained the junction of the latter with zinc oxide nanoparticles in order to evaluate their action and toxicity against breast carcinomas in female mice. X-ray and histological studies have shown that betaine-gallium tetrachloride is more toxic than the complex associated with zinc oxide nanoparticles, the latter being well tolerated and able to reduce the mammary carcinomas of the animals in the research, evidencing another antineoplastic alternative [16].

Maltol-3-hydroxy-2-methyl-4-pyrone compounds are excellent ferric ion chelators, and are widely used in iron deficiency anemias [55]. Because of this information, researchers developed gallium maltolate for oral use [26]. Gallium maltolate has emerged as an alternative to increase the bioavailability of $Ga^{3+}$ cation in the body. Tests were performed on dogs comparing the bioavailability of gallium maltolate with intravenous gallium nitrate, and tests with gallium maltolate in oral form in humans. Both results showed higher compound pharmacokinetic efficiency compared to gallium nitrate [56].

In addition, gallium maltolate has shown to have a high affinity for transferrin and low toxicity, which justifies its higher bioavailability in a safer manner [57]. Bernstein et al. [58] reported the experimental use of gallium maltolate in a liver cancer patient, achieving clinical improvement and reduction of liver tumor mass.

Collery et al. [54] reported the use of gallium tris-8-quinolonate III, also known as KP46, in patients with breast, colon and melanoma cancer, comparing it with

gallium chloride. KP46 has been shown to have an advantage in inhibiting cancer cell growth.

There are also reports of gallium-based compounds linked to thiosemicarbazones with antitumor action [59,60]. Arion et al. [61] were able to demonstrate in their experiments the retraction of breast and ovarian tumors. This action may be justified due to the great capacity of thiosemicarbazones, when associated with ferric ions, to inhibit the action of ribonucleotide reductase, and consequently inhibit DNA synthesis in cells. Due to its similarity to $Fe^{3+}$, $Ga^{3+}$ when associated with thiosemicarbazones has an effective therapeutic property [15].

Still under this theme of coordinating compounds, gallium associated with pyridines and phenolates showed encouraging results as described by Chen et al. that *in vitro* assays can stimulate the apoptosis process of malignant prostate cell strains [62]. Chitambar [26] describes some actions of gallium complexes, with similar therapeutic evidence described, such as: gallium-pyridone-hydrazone, gallium-azole compounds, gallium carboxylates and heterocyclic thiolates.

Several researchers are trying to improve the delivery of gallic drugs to living organisms. In 2012, Wehrung and Oyewumi developed the nanoparticulate synthesis of gallic hexadione and gallium acetylacetonate, which was obtained through binary mixtures using Gelucire® polymer, the system being solubilized in cetyl alcohol. The system was delivered to lung cancer cells to interfere with their mitochondrial metabolism. When compared to isolated gallium compounds, nanoparticles obtained more refined pharmacological profiles [63].

Still regarding technological improvements of gallic compounds, a group of researchers from India in 2016, developed the synthesis of the inclusion complex: gallium oxide hydroxide-β-cyclodextrin. After obtaining and physicochemical characterization of the compound, the researchers inserted it into HeLa strains in vitro, realizing that there was a marking of tumor cells, suggesting its use in PET-SCAN in the diagnosis of tumors [14].

Clinical investigations into the pharmacological profile of gallium nitrate revealed that it exhibited its strongest antineoplastic activity in the treatment of non-Hodgkin's lymphoma and bladder cancer. Gallium nitrate was used in patients with relapse of non-Hodgkin's lymphoma who did not respond to conventional chemotherapy drugs. Gallium nitrate does not produce myelosuppression and it can, therefore, be used in patients with low leukocyte or platelet counts. Also, it does not appear to share cross-resistance with other chemotherapists [41].

Lessa et al. [35] presented a review of gallium complexes with antitumor and antimicrobial properties. Among the antitumor properties, clinical trials have shown particular efficacy against bladder, urothelial and some lymphoma carcinomas.

Due to the need for a higher iron concentration for cancer cells, Firmino et al. conducted a study aimed at obtaining cytotoxic compounds that could promote iron metabolism disturbance in cancer cells. The compounds were formed with iron and hydrazone chelators (HPAmIH and PAmIH). The action of the complexes was tested against leukemia, breast cancer, colorectal carcinoma, prostate cancer, and nonmalignant human embryonic kidney cell lines. Ga (HAPIH) (APIH)] $(NO_3)_2 \cdot 2H_2O$ was the most cytotoxic compound, with colorectal carcinoma cells being the most susceptible. Both compounds inhibited the cell cycle and generated increased subploid DNA content of colorectal carcinoma cells after 24 hours of treatment, presenting a pro-apoptotic potential [24].

**Effects of hypercalcemia and bone metabolism:**
Malignant hypercalcemia affects patients causing various symptoms such as confusion, polyuria, coma and even death. It falls into four categories: multiple myeloma, parathyroid hormone-related excess, 1,25-dihydroxyvitamin D overproduction, and ectopic parathyroid hormone production [64]. Initial therapies include saline and intravenous bisphosphonate treatment to reduce bone destruction. As adjuvant therapies, corticosteroids, calcitonin and gallium nitrate may be used [65,66].

Gallium nitrate has already been approved by the Food and Drug Administration (FDA) for the treatment of malignancy-associated hypercalcemia [67]. Gallium in the form of citrate buffered gallium nitrate solution [$Ga(NO_3)_3$] (Ganite) is also approved by the FDA for the treatment of hypercalcemia [31].

According to the evidence on decreased blood calcium levels in a significant number of patients treated with gallium nitrate, investigations have been conducted to examine its potential as a treatment for cancer-associated elevated blood calcium levels. Studies have shown that continuous gallium nitrate infusion is effective in controlling high blood calcium levels [41].

Characterized by an increase in serum calcium level, malignant hypercalcemia is quite common in advanced cancer stages. These patients are typically symptomatic and require urgent treatment. Some treatment options include IV hydration, calcitonin, bisphosphonates, denosumab, and gallium nitrate. The latter presents its action by inhibiting osteoclastic activity and increasing kidney calcium clearance. In addition to demonstrating good tolerability and a small percentage of treatment-induced anemia, gallium nitrate proved to be more potent than calcitonin; however, in 2012, gallium nitrate production was discontinued, making treatment for this pathology unavailable [68].

Although its mechanism of action has not been completely elucidated, gallium nitrate may inhibit bone resorption by osteoclasts [69]. For the treatment of malignant hypercalcemia, the recommended effective dose is 200 mg/m$^2$/day for 5 days [70].

Osteoporosis affects bone fragility due to its mass reduction, resulting in fractures [71]. Biophosphonates are the therapies of choice to treat this condition, but they have some disadvantages regarding adverse events, negatively affecting treatment adherence. Given this problem and considering its anti-resorptive properties, gallium would be a potential drug. Innovative strategies using calcium phosphate (CaP) biomaterials as Drug Delivery System (DDS) have been proposed in association with gallium to strengthen osteoporotic sites, providing biomaterials (CaP) that can promote bone growth and release specific drugs capable of controlling excessive activity of osteoclast resorption. When released from DDS, gallium is likely to attach to bone tissue through its affinity for hydroxyapatite, but further *in vivo* studies need to be performed [72].

Due to its many properties as a bone resorption inhibitor, gallium can influence osteoporosis healing. Researchers have synthesized organic gallium (OG), which is formed through a mixture of gallium and yeast. Results show that OG may increase bone volume and area, cortical thickness, trabecular thickness and may decrease the number of osteoclasts in the osteoporotic invoice, evidencing that the obtained data allow the OG to heal osteoporotic fractures [73].

**Immunosuppressive and anti-inflammatory agents:**

Some preclinical studies available in the literature show results on the use of gallium nitrate and other gallium-based compounds and their effects on the immune system and inflammatory processes [29]. In vivo studies show that gallium accumulates at sites of inflammation and exhibits anti-inflammatory and immunosuppressive activity [56]. Other research conducted in animal models has shown that gallium nitrate can suppress inflammatory arthritis, experimental autoimmune encephalomyelitis, lupus, cardiac allograft rejection, and graft versus host disease in experimental bone marrow transplantation [74,75,76,77,78,79].

Gallium maltolate, gallium-based formulation, increased the production of interferon-γ-IL-13-induced chemokines, but decreased IL-10 production in HUT lymphoma cells [80]. The impact of gallium maltolate on cytokines may be relevant to the pathophysiology of lymphoma, as these cutaneous lymphomas may arise from a background environment of chronic inflammation [81].

In clinical trials, a 14% aqueous solution of gallium nitrate, when topically administered to patients' arthritic hands, led to a reduction in pain and inflammation. Oral treatment (50 mL of a 1% gallium nitrate solution) in osteoarthritis patients resulted in almost complete elimination of pain. Treatment of shoulder joint stiffness with 40% topical gallium nitrate resulted in pain reduction/complete restoration of movement and absence of pain for more than one year after treatment [82].

Possible suggested mechanisms of action included anti-inflammatory activity, improved bone density, and antibacterial effects. Thus, studies indicate that gallium may be effective in treating arthritis pain and inflammation. The indication of the use of gallium nitrate as modulator of inflammation in arthritis may be due to its inhibition in the activities of interleukin-1-beta and matrix metalloproteinases [82].

Gallium (III) has shown inhibition of the production of inflammatory cytokines such as interleukin-1-beta produced by macrophage-like cells, according to *in vitro* studies. Gallium (III) has been reported to be effective in the treatment of *Mycobacterium butycicum*-induced arthritis in rats. Long-term elimination of arthritis pain by gallium (III) was first observed in horses being treated primarily for navicular disease [82].

Bernstein evaluated the oral anti-inflammatory effects of gallium maltolate in rats presenting inflammatory arthritis. Among this inflammatory condition, two categories of arthritis were investigated, the adjuvant-induced and chronic arthritis. Gallium maltolate was

able to reduce inflammatory joint conditions, bone degradation, enlargement of the liver and spleen, and other dose-dependent inflammation measures. It can also be seen that, in some activities, gallium maltolate was more effective than the immunosuppressive drug dexamethasone or cyclosporine [83].

**Antimalarial agent:**

Malaria is a parasitosis caused by the protozoan of the genus *Plasmodium*, within this genus the species responsible for causing the most severe form of malaria in humans is *Plasmodium falciparum* [84]. Among the existing drugs for treatment, the one of choice for prevention and treatment of malaria is chloroquine, which acts in the erythrocytic phase of parasitosis. However, due to the large mutation capacity of the parasite that triggers resistance to antimalarial treatment, this parasitosis has become a problem. In this context, the development of new antimalarial chemotherapies is necessary [85,86,87].

Malaria parasite produces heme due to hemoglobin degradation. Free heme is toxic to cells so detoxification is required due to the crystallization of heme into hemozoin. B-hematin polymerization has been shown to prevent heme toxicity as the primary target of antimalarial therapy and the main mechanism of action of chloroquine [85,88].

Metalloporphyrins are potent heme-polymerization inhibitors and the central ion plays a major role in the inhibitory action of metalloporphyrins. Begum et al. [88] evaluated the in vitro antimalarial activity of 10 different metalloporphyrins including 4 gallium derivatives: gallium protoporphyrin IX (GaPPIX), gallium salt protoporphyrin IV (GaPPIXNa2), gallium deuteriopropyrin (GaDPIX) and hematopyrin gallium (GaHPIX). The results showed that all were effective in inhibiting heme polymerization, however GaPPIX and GaDPIX showed more significant results during in vitro tests, presenting $IC_{50}$ values below 80 µM in the trophozoite form of *Plasmodium falciparum* [85,87].

Studies have shown that gallium (III) complexes have action against *Plasmodium falciparum*. A study by Goldberg et al. identified a new class of hexadentylated ethylenediamine compounds -N, N * - bis [propyl (2-hydroxy (R) -benzylamino)] - metal (III) [(R) -ENBPI- M (III)] coordinated by the metals Al (III), Fe (III) and Ga (III), which formed racemic mixtures with antimalarial activity. Among them, 4,6-dimethoxy-ENBPI Ga (III) showed a potent inhibition of growth of the HB3 culture as well as heme polymerization, while that consisting of 3-methoxy-ENBPA Ga (III) showed selective action for chloroquine resistant parasites [89].

Subsequently, Sharma et al. developed a gallium (III) aminophenol complex, [{1,12-bis (2-hydroxy-3-methoxybenzyl) -1,5,8,12-tetraazadodecane} gallium (III)] [Ga (madd)] +, which shows potent antimalarial action in chloroquine resistant organisms, selectively against *Plasmodium falciparum* chloroquine resistant Dd2 clones, directly inhibiting heme group polymerization, two to three times more potent than chloroquine under the same conditions, since gallium (III) has similar chemical coordination as iron (III) [90].

Ocheskey et al. [91], analyzing the structure-activity relationship of the complex previously studied by Sharma et al. found that a simple variation in the position of methoxy groups in the ligand aromatic rings, transforming the compound into [h1,12- bis (2-hydroxy-5-methoxybenzyl) -1,5,8,12-tetraazadodecane-gallium (III)] + [Ga-5-Madd] +, was able to alter selectivity, previously selective against clones Dd2 and became selective against *Plasmodium falciparum* chloroquine sensitive HB3 clones [90].

In 2005 a new antimalarial compound was synthesized, [{1,12-bis (2-hydroxy-3-methoxy-5-(quinolin-3-yl) -benzyl) -1,5,8,12-tetraazadodecane } - gallium (III)] +, [Ga-3-M-5-Quadd] + for a safe and effective compound, with low cost, short synthetic routes and that can overcome resistance. The results showed that the $IC_{50}$ value in the chloroquine-sensitive HB3 clone with [Ga-3-Madd] + was 20 µM, whereas in the quinoline-incorporated metallo-antimalarial the $IC_{50}$ was 0.6 µM indicating a good improvement in its efficacy by 0.33 times. However, in chloroquine-resistant Dd2 clones, there was no significant improvement, with a small change in the IC50 from 1.8 µM to 1.4 µM [92].

Harpstrite et al. performed the chemical characterization of new gallium (III) metalloantimalarial compounds with an aminophenol binder as a substitute for iron (III), called [{1,12-bis (2-hydroxy-3-ethyl) -benzyl) -1,5,8,12-tetraazadodecane} metal (III)] +, [M-3-Eadd] + [M = iron (III); gallium (III)] and act similarly to chloroquine, inhibiting the formation of hemozoin. Evidencing that the substitution of iron (III) by gallium (III) can happen in biological environment due to the similarity of coordination, stability and cytotoxicity between ions [93].

A gallium (III) complex with 7-chloroquine thiosemicarbazone was synthesized and characterized by Kumar et al. with anti-malaria efficacy, which showed the same percentage of inhibition of *Plasmodium falciparum* as lumefantrine but in lower concentration, comparing the $IC_{50}$ of the 250 nM ligand to the $IC_{50}$ of the 173 nM gallium complex, suggesting increased antimalarial efficacy of the complex due to coordination with gallium [94].

Yan et al. developed in China a new alpha-dimethylamino-cyclohexoxyl-dimethyl gallium antimalarial drug (DCDG). In vivo studies using rats were performed to verify the efficacy against *Plasmodium berghei* and *Plasmodium yoelii* by comparing DCDG, chloroquine and artemisinin with doses of respectively 1–3, 40–80 and 200–400 mg/kg, respectively. And show that DCDG was able to kill malaria parasites quickly, they observed that large autophagic vacuoles containing some membranous materials were formed, which were subsequently extruded, leaving the parasite more concentrated, picnotic and causing its death, acting differently from chloroquine and artemisinin [95].

## CONCLUSION:

Although gallium is not part of cellular physiology, it has chemical properties that mimic iron, providing the absorption of gallium by microorganisms and tumor cells due to interaction with various biological processes. Gallium and its complexes show promising pharmacological options for various diseases, as reported in this article. Gallium complexes represent a major breakthrough in therapy as they have potential for new drug candidates. Although their pharmacological properties have been investigated and shown relevant results in preclinical tests, the continuation with clinical studies of these complexes is of great importance in order to better elucidate their mechanisms of action.

**Conflicts of interest:**

The authors declare no conflicts of interest in the elaboration of this article.

**Financial & competing interests disclosure:**

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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