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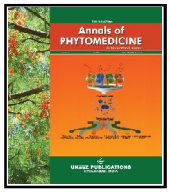

Review Article : Open Access

A comprehensive review on benzimidazoles: Current and future perspectives

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Abstract

The multi-targeted approach is critically prompting the researcher and the healthcare system to the development of newer pharmaceuticals that can obviate the lack of a multi-targeted therapeutic approach for alleviating acute and chronic ailments. Benzimidazole or plants derived benzimidazole or their derivatives have contributed an immense role in the alleviation of target-based multiple pathogenesis due to their unique chemical nature as well as molecular pattern. The review gathers a comprehensive note on the benzimidazole and their biological aspects. The information was gathered from different electronic databases published articles on national and international platforms. Each screened article was finalized for impactful information through experts and drafted as a systematic report that contributed to the chemistry and pharmacology of benzimidazole. The findings conclude that benzimidazole can be the most effective and multi-target-based lead to mimic the pathogenesis associated with acute and chronic ailments, hence contributing to further accelerating the accessibility in the promotion of pharmaceuticals and the healthcare system.

1. Introduction

Since history, various pharmaceutical agents have been developed, in which natural resources especially medicinal plants have contributed majorly to drug discovery and development and thus treating many acute and chronic ailments (Amrutanand *et al*., 2021; Mehrotra, 2020). Benzimidazole (BMZ) has been acknowledged as the most effective drug molecule with a multi-targeted therapeutic effect and is characterized as a heterocyclic aromatic compound comprised of benzene and imidazole ring fused (Pathare and Bansode, 2021). The H-atom in benzimidazole is sandwiched between the double- and single-bonded N-atoms to produce two chemically equivalent tautomers, which can be represented by two sets of numbers to indicate the position of the substituents group, such as 6-methylbenzimidazole, if the benzimidazole is an N-substituted derivative and produces two isolated isomers. Due to the amphoteric nature of the N-atoms, they both exhibit acidic and basic characteristics (Marinescu, 2021; Pathare and Bansode, 2021). It is preferred to the macromolecule and entitled to the pharmacophore in medicinal chemistry. The benzimidazole antimicrobials were first introduced in the late 1960s to control plant diseases, and they gained widespread acceptance relatively fast. This was because of their special qualities, which included greater efficacy at low application rates, excellent crop safety, and the capacity to shield the crop's new growth due to their systemic activity (Leadbeater, 2014).

It is allied with the various types of pharmacokinetics and pharmacological properties (Salahuddin *et al*., 2017), benzimidazole scaffold has been contributed to different types of compounds which act as potential therapeutic agent such as anticancer, antihypertensive, CNS stimulants, antiparasitic, antiviral, and antimicrobial as well as antidepressants has made it beneficial for the headway of the many therapeutic agents (Kaur and Silakari, 2018; Tahlan *et al*., 2019).There are various benzimidazole derivatives of various moiety such as albendazole, mebendazole, lansoprazole, omeprazole, pantoprazole, thiabendazole, rabeprazole, timoprazole, and mebendazole, widely used for the anthelmintic food and drug administration (FDA) approved drugs present in the market (Vashist *et al*., 2018). The first benzimidazole is created by Hoebreckerin 1872 by utilizing 2-nitro-4-methylace-tanilide to produce 2, 5 (or 2, 6)-dimethylbenzimidazole.There are varieties of benzimidazole that leads to the compounds such as purine, histidine, histamine, and a nucleic acid and occupied a unique place in the field of medicinal chemistry as well as pharmacology (Faheem *et al*., 2020). Moreover, hundreds of benzimidazole derivatives have been synthesized to explore synthetic drug discovery strategies as well as to investigate the new therapeutic agents for the treatment of severe diseases such as cancer, arthritis, HIV, *etc*. Benzimidazole derivatives are used in various ways such as analgesic, antiviral, anti-inflammatory, antifungal, anti-helminthic, antibacterial, antimicrobial, anticonvulsant, anticancer, and antihypertensive (Lead beater, 2014; Pathare and Bansode, 2021).

In recent times, benzimidazole has been acknowledged as the choice of moiety due to their role in different disease. Furthermore, it has been characterized as the main lead against the survivability of the different gram-positive and gram-negative strains and even acts as an effective therapy against the antibacterial agents that causes bacterial resistance. Taking all these influences into consideration and their emergence in further validation and repurposing of benzimidazole, the study is targeted to explore the present evidence on benzimidazole and its derivatives for their respective reported

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pharmacological activities. The review focused on the major derivatives of benzimidazole and reported their pharmacological activitiesfor further exploration of scientific facts about benzimidazole.

2. Review findings

2.1 Benzimidazole

With the substitution of fluorine, propylene, tetrahydroquinoline, and cyclic molecules in diverse benzimidazole derivatives in 1990, more stable, bioavailable, and biologically active chemicals were produced. In 1991, compounds were created by substituting a long chain of propyl acetamido thio, thiazole-amino, tetramethyl piperidine on pyridine and derivatizing the N-H of benzimidazoles by an electron-donating group. This process led to the development of derivatives that exhibited good antiulcer action. Later compounds created by substituting dimethyl imidazopyridine in the benzimidazoles' sixth position had potent antisecretory action. (Brishty *et al*., 2021; Leadbeater, 2014). The tautomerism phenomenon of benzimidazole has been depicted in Figure 1.

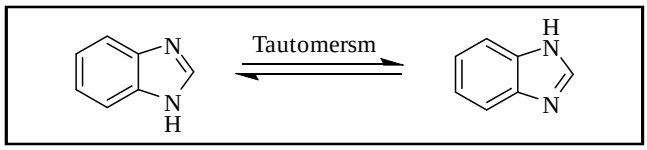


Figure 1: Tautomeric forms of benzimidazole.

Pyridine's -CH_3 group is used to synthesise pantoprazole for its high biological activity (Patil *et al*., 2008). the addition of a stiff ring to benzimidazoles, which is then modified in acidic environments to produce a biologically active sulfenamide. Triazole 3-yl 1-3 di-thio was used in place of the pyridine and demonstrated promise when tested physiologically against *H. pylori*. Pyrimidine was used as a ring substitution in another method to lessen the basicity of the pyridine ring nitrogen and the irreversibility of the molecule with the enzyme. When pyridine was substituted with phenyl isobutyl methyl amine, laminiprazole was created. Its powerful proton pump inhibitory action was first described in 1996 (Brishty *et al*., 2021; Leadbeater, 2014). A 2,2 dimethyl pyrranopyridine ring also takes the place of the pyridine. With the use of his own creation, 2-dimethyl amino thiazocyclobenzene benzimidazole, he demonstrated strong proton pump inhibitory activity. The pyrrolo-benzimidazole moiety, which exhibited proton pump inhibitory action, took the place of pyridine in 1998. Strong antiulcer action was found for the synthesis of esomeprazole by asymmetric oxidation of the prochiral sulphide of omeprazole (Patil *et al*., 2008). It has been established that among the various benzimidazole molecules, the substances adenine and guanine, along with their two of the five nucleic acid bases, such as uric acid and caffeine, serve as the foundation for a variety of benzimidazoles-derived constituents. Given this fundamental structural similarity, it should come as no surprise that the benzimidazole nucleus has significantly aided in the creation of a wide range of benzimidazole derivatives and their role in the treatment of disease. It is also regarded as a crucial pharmacophore with a privileged structure in medicinal chemistry (Ates-Alagoz, 2013; Yadav *et al*., 2016). Primary leads of benzimidazole biomolecules containing heterocyclic ring has been respresented in Figure 2.

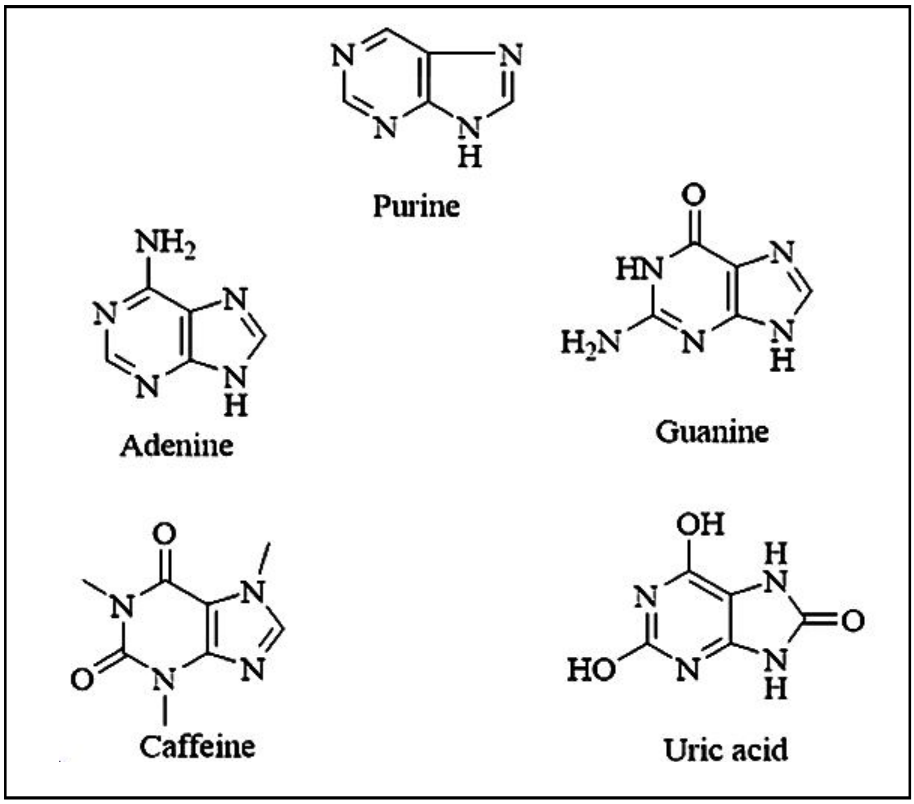


Figure 2: Primary leads of benzimidazole biomolecules containing heterocyclic ring.

2.2 Natural benzimidazole

Natural resources were crucial for developing new classes of antibiotics with innovative antibacterial scaffolds. Berberine, a naturally occurring isoquinoline alkaloid, has been employed for many years to treat inflammatory disorders such bacillary dysentery, diabetes, acute gastroenteritis, and cholera. It was first discovered in the medicinal herbs *Berberis vulgaris*, *Tinospora cordifolia*, and *Rhizomacoptidis* (Gaurav *et al*., 2020a; Kamrani Rad *et al*., 2017). Currently, berberine is being used in a variety of clinical settings, particularly for antibacterial purposes. Research has shown that berberine with quaternary nitrogen, polycyclic, and planar systems helps to resist the viability of bacterial strains by distorting cellular permeability and causing DNA damage (Peng *et al*., 2015). Because of its exceptional structural characteristics, natural berberine is a novel, potential scaffold for the development of antibacterial drugs in the future. Due to the purine-like structure in the benzimidazole ring and the ability of benzimidazole derivatives to prevent, the production of proteins and nucleic acids, benzimidazoles in particular have drawn a lot of attention. Many bactericides have been commercialized that contain benzimidazole fragments, including carbendazim and thiabendazole, displaying tremendous antibacterial potential (Sun *et al*., 2021). BMZ has demonstrated potential bioactivity when anchored with another heterocyclic substance, such as triazole, morpholine, thiadiazole, piperazine, oxadiazole, or piperidine. The generated derivatives' lipophilic characteristics are improved by the sulfonamide moieties that are present inside the heterocyclic template (Daci-Ajvazi and Govori, 2013). Several benzimidazole derivative has been represented for the various activities and some of them has been represented in Figure 3.

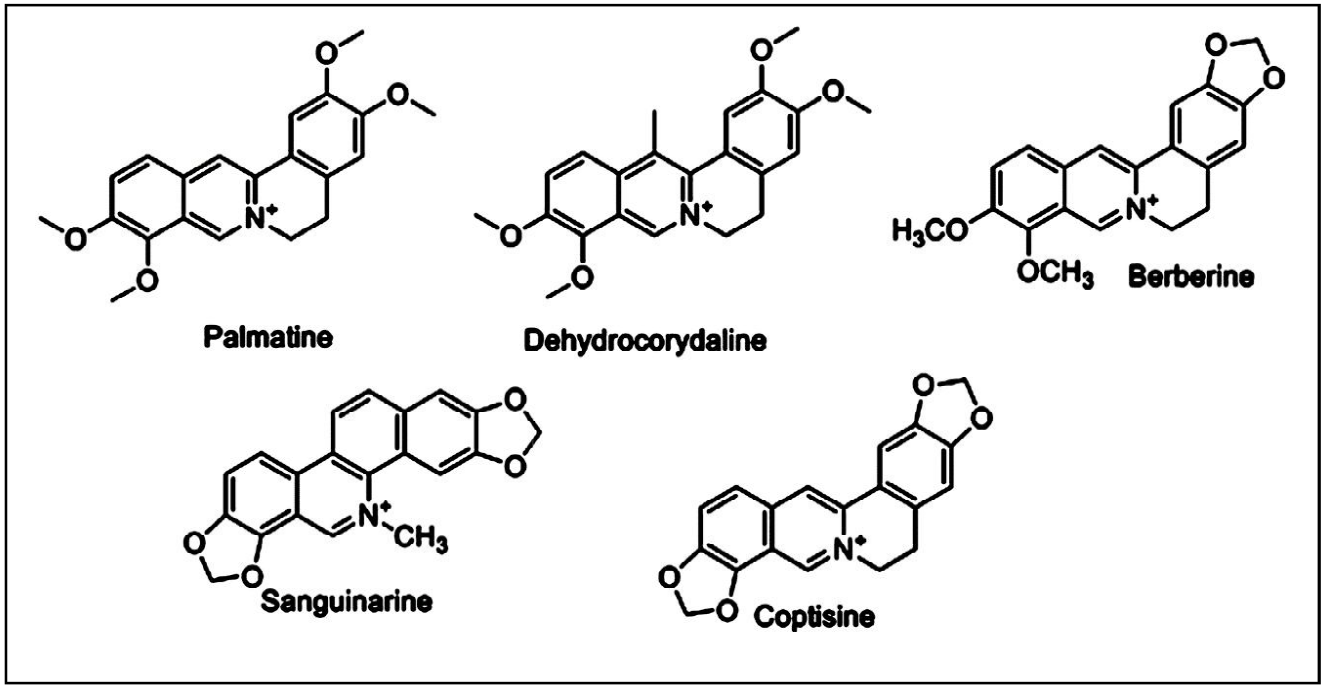


Figure 3: Chemical structure of some natural constituents having benzimidazole like structure.

2.3 Expert opinion on plant derived benzimidazole

Antibacterial, antiviral, anticancer, antitubercular, anti-inflammatory, herbicidal, fungicidal, analgesics, insecticidal, antihypertensive, antidiabetic, and other applications are only a few of the many uses for heterocyclic compounds. Some of these heterocyclic compounds, which exhibit a variety of solvatochromic, photochromic as well as biochemical luminescence properties, are abundant in natural sources such as plant alkaloids, haemoglobin, anthocyanins, and flavones and are essential for human survival as medications, vitamins, dyes, amino acids, and enzymes (Brishty *et al*., 2021). For the past two decades, across heterocyclic chemicals, benzimidazole derivatives have played the most exciting and eye-catching pioneering roles in the synthetic pharmaceutical and agricultural sectors. The benzimidazole compounds can readily interact with a variety of biomacromolecules or target proteins due to the nucleus of the benzimidazole being comparable to numerous naturally occurring nucleotides and being present in a number of natural substances. As a result, the substances formed from the benzimidazole ring system have broad-spectrum effectiveness against a variety of human diseases, including cancer, hypertension, diabetes, infections from bacteria or viruses, inflammation, gastritis, and neurological diseases (Brishty *et al*., 2021). There are several natural components which having similar heterocyclic ring like benzimidazole as showed in Figure 3.

2.4 Benzimidazole pharmacological activities

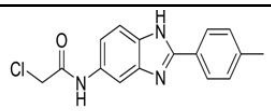
2.4.1 Anticancer activity

The biological activities of benzimidazole derivatives include anticancer activity. However, the anticancer mechanism of benzimidazole, a unique 2-aryl benzimidazole derivative, against carcinoma is largely unclear. Its chemical name is 2-chloro-N-(2-p-tolyl-1H-benzo[d]imidazol-5-yl) acetamide and its molecular weight is 299 ($C_{16}H_{14}C_lN_3O$). By lowering EGFR and HER2 tyrosine phosphorylation and preventing the downstream activation of the

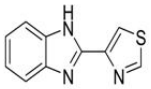
PI3K/Akt and MEK/Erk pathways *in vitro* and *in vivo*. In this study, it was showed that 5a effectively suppressed both EGFR and HER2 activity. Additionally, it was found that benzimidazole boosted FOXO translocation from the cytoplasm to the nucleus and blocked FOXO phosphorylation, which captured cells in the G1 phase of the cell cycle and caused death. Additionally, by upregulating the death receptor in cancer cells and activating the c-Jun N-terminal kinase (JNK), benzimidazole effectively promoted apoptosis. Additional findings showing that benzimidazole dramatically decreased tumor volume were consistent with the anticancer action of benzimidazole (Chu *et al*., 2015). Yadav *et al*. (2016) explain the therapeutic significance and repurposing of benzimidazoles, specifically thiabendazole, astmizole (antihistaminic), flubendazole (anthelmintic), lansoprazole, and omeprazole (antiulcerative) for anticancer activity. They reported that this category of benzimidazoles is particularly active against cell lines such as MCF-7 (breast), and thus acting against proliferation of the cells (Yadav *et al*., 2016).

It has been reported that the putative bioactive molecule berberine has outstanding therapeutic benefits. Up to this time, a great deal of research has been done on the anticancer effects of berberine. In the current review, the key details regarding this compound's prospective anticancer effect are compiled. Studies on the therapeutic efficacy of berberine have been conducted on cancers of the colon, breast, pancreatic, liver, oral, cutaneous, prostate, intestinal, and thyroid. To inhibit the spread of cancer cells, berberine induces apoptosis, controls the cell cycle, and encourages autophagy. Berberine also inhibits tumor cell invasion and metastasis by lowering the expression of proteins connected to metastasis. It reduces the rate of ecto-mesenchymal transition protein synthesis (Rauf *et al*., 2021).

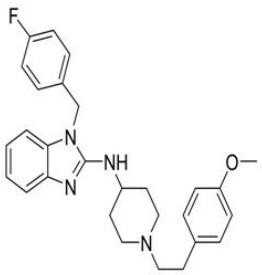
A natural substance called sanguinarine (SNG) possess benzimidazole like structural similarity has a wide range of pharmacological effects, offers remarkable medical applications against a variety of disorders, including cancer. SNG showed antiproliferative capability against BCPAP as well as TPC-1, two well-known papillary thyroid cancer (PTC) cell lines. PTC cells' cell proliferation was markedly reduced by SNG in a dose- and time-dependent manner. Western blot examination showed that SNG treatment of PTC cells resulted in the activation of caspase-3 and caspase-8, which significantly decreased the unregulated production of p-STAT3 without changing total STAT3 and prevented the proliferation of PTC. The autophagy markers are activated, and PARP is cleaved. Additionally, N-acetyl cysteine (NAC), an antagonist of ROS, reduced SNG-mediated antiproliferative, apoptotic, and autophagy producing action in PTC cells, demonstrating that SNG-mediated chemotherapeutic actions in PTC cells included the formation of reactive oxygen species (ROS) (Khan *et al*., 2020).



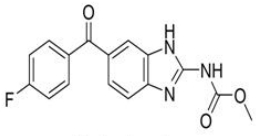
2-chloro-*N*-(2-(*p*-tolyl)-1*H*-benzo[*d*]imidazol-5-yl)acetamide
Chemical Formula: $C_{16}H_{14}ClN_3O$
Exact Mass: 299.08
Molecular Weight: 299.76
m/z: 299.08 (100.0%), 301.08 (32.0%), 300.09 (17.3%), 302.08 (5.5%), 301.09 (1.4%), 300.08 (1.1%)
Elemental Analysis: C, 64.11; H, 4.71; Cl, 11.83; N, 14.02; O, 5.34



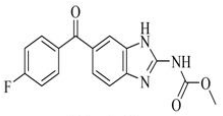
Thiabendazole
4-(1*H*-benzo[*d*]imidazol-2-yl)thiazole
Chemical Formula: $C_{10}H_7N_3S$
Exact Mass: 201.04
Molecular Weight: 201.25
m/z: 201.04 (100.0%), 202.04 (10.8%), 203.03 (4.5%), 202.03 (1.1%)
Elemental Analysis: C, 59.68; H, 3.51; N, 20.88; S, 15.93



Astemizole
1-(4-fluorobenzyl)-*N*-(1-(4-methoxyphenethyl)piperidin-4-yl)-1*H*-benzo[*d*]imidazol-2-amine
Chemical Formula: $C_{28}H_{31}FN_4O$
Exact Mass: 458.25
Molecular Weight: 458.58
m/z: 458.25 (100.0%), 459.25 (30.3%), 460.25 (2.7%), 460.25 (1.7%), 459.25 (1.5%)
Elemental Analysis: C, 73.34; H, 6.81; F, 4.14; N, 12.22; O, 3.49

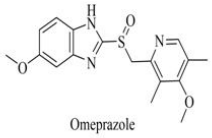


Flubendazole
methyl (6-(4-fluorobenzoyl)-1*H*-benzo[*d*]imidazol-2-yl)carbamate
Chemical Formula: $C_{16}H_{12}FN_3O_3$
Exact Mass: 313.09
Molecular Weight: 313.29
m/z: 313.09 (100.0%), 314.09 (17.3%), 315.09 (1.4%), 314.08 (1.1%)
Elemental Analysis: C, 61.34; H, 3.86; F, 6.06; N, 13.41; O, 15.32



Flubendazole

methyl (6-(4-fluorobenzoyl)-1*H*-benzo[*d*]imidazol-2-yl)carbamate
Chemical Formula: $C_{16}H_{12}FN_3O_3$
Exact Mass: 313.09
Molecular Weight: 313.29
m/z: 313.09 (100.0%), 314.09 (17.3%), 315.09 (1.4%), 314.08 (1.1%)
Elemental Analysis: C, 61.34; H, 3.86; F, 6.06; N, 13.41; O, 15.32



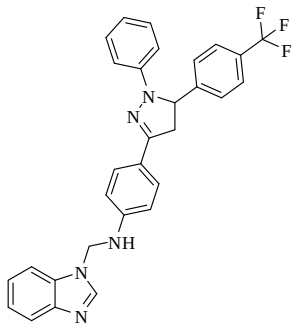
Omeprazole

5-methoxy-2-(((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)sulfinyl)-1*H*-benzo[*d*]imidazole
Chemical Formula: $C_{17}H_{19}N_3O_3S$
Exact Mass: 345.11
Molecular Weight: 345.42
m/z: 345.11 (100.0%), 346.12 (18.4%), 347.11 (4.5%), 347.12 (1.6%), 346.11 (1.1%)
Elemental Analysis: C, 59.11; H, 5.54; N, 12.17; O, 13.90; S, 9.28

Figure 4: Anticancer benzimidazole derivatives and their chemistry.

2.4.2 Antibacterial activity

As we are aware with the varieties of the pathogens and the progressive antibacterial resistance to the modern medicines, some of the potential antibacterial agents is critically needed to obviate the paucity antibacterial agents (Kiran *et al*., 2021). Bacterial induced oxidative stress and inflammation is also concerning to developed the multi-mechanistic and therapeutic agents for treating bacterial infection induced inflammation and oxidative stress (Ali *et al*., 2022).The benzimidazole-hydrazone synthesized derivatives have been reported for their potential antibacterial effect. In a study conducted by Krishnanjaneyulu *et al*. (2014) evaluated the anti-bacterial effect of several unsubstituted derivatives of benzimi dazole and based on the findings it is reported that compound N-((1H-benzoimidazol-1-yl) methyl)-4-(1-phenyl-5-(4-(trifluoro methyl) phenyl)-4,5-dihydro-1H-pyrazol-3-yl) benzenamine 5i exhibited significant antibacterial effect against several gram-positive and gram-negative bacterial strains and the activity was found comparable with the standard drugs. Hence, it was reported that the afore mentioned compound can be a potential candidate as an antibacterial for broad-spectrum bacterial infection or their associated complications (Krishnanjaneyulu *et al*., 2014). Özkay *et al*. (2011) evaluated the antibacterial effect of some benzimidazole-hydrazone compounds against gram-positive bacterial strains; namely, *Staphylococcus aureus*, *Enterococcus faecalis*, *Bacillus subtilis* and *Listeria monocytogenes* as well as simultaneous evaluation of antifungal activity against *Candida* species. The results showed the tested compounds exerted least antibacterial effect then the effect of antifungal activity. Therefore, it can be concluded that benzimidazole-hydrazone compounds are comparatively more effective than the standard drug concerning antibacterial effect (Özkay *et al*., 2011).



N-((1*H*-benzo[*d*]imidazol-1-yl)methyl)-4-(1-phenyl-5-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)aniline
Chemical Formula: $C_{30}H_{24}F_3N_5$
Exact Mass: 511.20
Molecular Weight: 511.55
m/z: 511.20 (100.0%), 512.20 (32.4%), 513.21 (5.1%), 512.20 (1.8%)
Elemental Analysis: C, 70.44; H, 4.73; F, 11.14; N, 13.69

Figure 5: Antibacterial benzimidazole derivative and its chemistry.

2.4.3 Antiulcer drugs

The aggressive and cytoprotective effects of acid and pepsin are generally agreed to be inequitable, which results in peptic ulcers. By preventing the release of acid and pepsin, histamine H2 receptor antagonists like cimetidine, ranitidine, and famotidine are frequently used to treat gastric duodenal ulcers. Proton pump inhibitors like omeprazole and pantoprazole are very successful at treating gastric duodenal ulcers because they stop the production of acid. However, it has been noted that recurrence of peptic ulcers is generally high even after long-term therapy has healed them, and that frequent use of H2 receptor antagonists and proton pump inhibitors may erode the protective mechanisms of the gastric mucosa (Tanaka *et al*., 2004). Six novel benzimidazole-pyrazole hybrid compounds were created by Noor *et al*. (2017) and Albino rats were used to test the molecules' *in vivo* antiulcerogenic properties. At a dose of 500 g/kg bw, these new hybrid compounds demonstrated equivalent anti-

ulcer potential in the range of 72-83%. At a dose level of 30 mg/kg, omeprazole showed the most antiulcer efficacy, with an 83% success rate. It was therefore reported that novel benzimidazole-pyrazole hybrids could be a contender for antiulcer drugs (Noor *et al*., 2017).

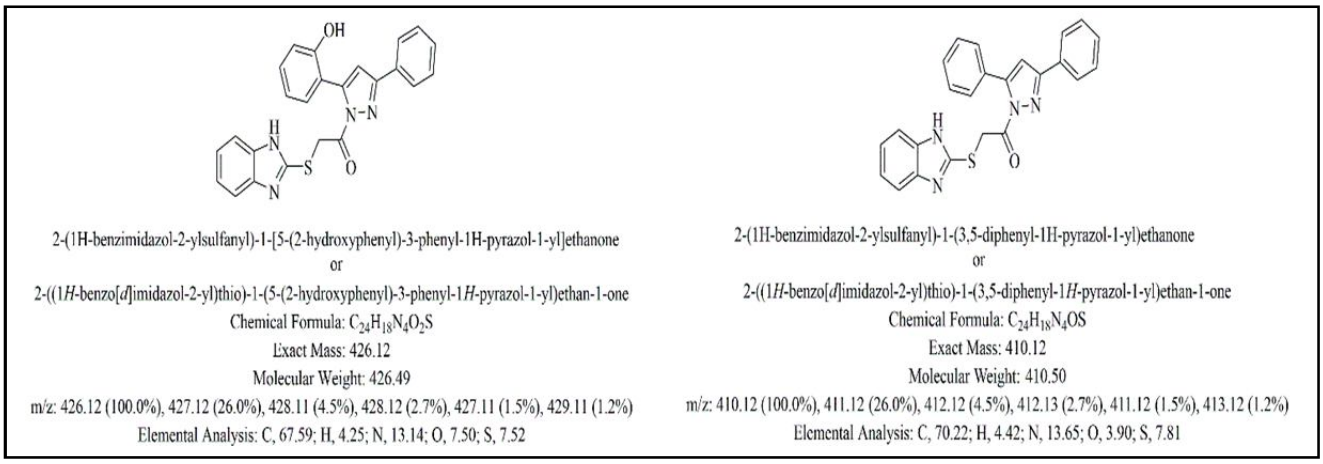


Figure 6: Antiulcer benzimidazole derivatives and their chemistry.

2.4.4 Antifungal Activity

There has been an increase in antifungal drugs in human medicine for alleviation of several acute and chronic ailments including the AIDS epidemic. Several studies have been conducted for the development of newer/novel benzimidazole and associated derivative which can act as the prominent antifungal agent, and thus treat acute and chronic fungal infection. In a study conducted by Khabnadideh *et al*. (2012) evaluated the antifungal effect of benzimidazole, benzotriazole, and aminothiazole derivatives against *Candida, Aspergillus,* and some species of dermatophytes. The findings showed that among the different benzimidazole compounds tested against the afore mentioned fungal strains, the compound 1-nonyl-1H-benzimidazole and 1-decyl-1H-benzimidazole exhibited the most prominent effect as antifungal activities. Furthermore, it was established that the compounds such as benzimidazole derivatives can be the established even far better antifungal agent than benzotriazole derivatives, and piperazine analogs for alleviating acute and chronic pathogenesis induced by fungal infection via regulation the fungal onsets (Khabnadideh *et al*., 2012). Elnima *et al*. (1981) evaluated *in vitro* antifungal activities of six benzimidazole and benzoxazole derivatives were tested against *Candida albicans*. It was found that out of six compounds, only compounds II and III (both benzoxazoles) were found biologically active with minimal inhibitory concentrations for 90% inhibition and it was revealed that the compounds such as benzoxazoles can work as the most active antifungal agent (Elnima *et al*., 1981). Chandrika *et al*. (2016) evaluated the antifungal activities of 18 alkylated mono-, bis-, and trisbenzimidazole derivatives against *Aspergillus* and *Candida*. The results of the study showed that out of 18 synthesized benzimidazole compounds, bisbenzimidazole compounds revealed moderate to excellent antifungal activities and the activity of the tested compounds was found comparable against the effect of fluconazole, itraconazole, posaconazole, and voriconazole which were used as the standard drug (Chandrika *et al*., 2016).

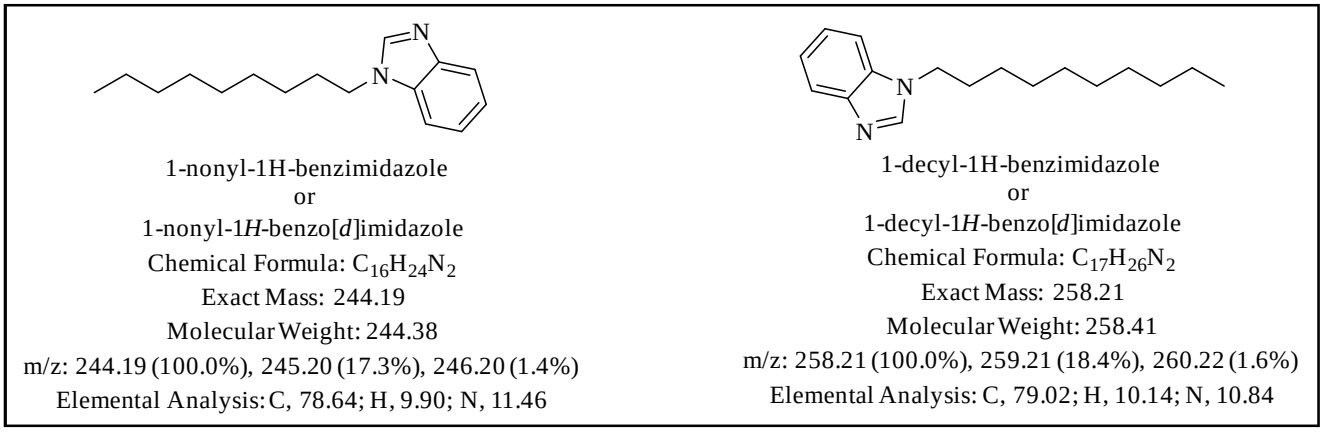


Figure 7: Antifungal benzimidazole derivatives and their chemistry.

2.4.5 Anti-inflammatory

Benzimidazole derivatives exhibiting an immense role in the alleviation of several inflammatory cytokines lead to severe inflammation and cause severalpathogeneses, intrinsically. Till date, the study for exploration on benzimidazole to unravel the criticism even opacity for development of the potent anti-inflammatory agents still on move. Benzimidazoles suggest that the propensity and position of the substitutions on the benzimidazole ring contribute significantly to the anti-inflammatory activity.

Benzimidazole and imidazopyridine compounds were tested for their ability to inhibit the production of pro-inflammatory cytokines in LPS-stimulated macrophages in a study by *Chen et al.* (2013). The study's findings demonstrated that imidazopyridine is a potent inhibitor of inflammatory cytokine expression. The compounds codded as X10, X12, X13, X14, and X15 strongly inhibited to imitate the actin of TNF- and IL-6 release out of 32 synthetic derivatives of benzimidazole. The expression of TNF- and IL-6 was found to be inhibited by those compounds in a dose-dependent manner, but compound X12 exhibited no cytotoxicity in hepatic cells. Furthermore, LPS-induced septic death was found significantly reduced in mouse models. Hence, it was concluded that new benzimidazole and imidazopyridine derivatives contribute an immense role in the pathogenesis induced by acute inflammation (Chen *et al.*, 2013). Pan *et al.* (2017) synthesized a series of benzimidazole analogs of thiabenzole and evaluated for their anti-inflammatory action against NLRP3 (nucleotide-binding domain leucine-rich repeat-containing protein family of pyrin domain) inflammasome using *in vitro* approaches. the outcome of that study showed that among several synthesized derivatives, two benzimidazole analogs of thiabenzole derivatives codded TBZ-09 and TBZ-21, exhibited significant potential against the excessive expression of IL-1β while other derivatives were found to exhibit comparatively lower effect and dose-dependent manner against the expression of IL-1β (Pan *et al.*, 2017).

Inflammation has been characterized as the response of immune system against exogenous and endogenous stimulus *via* production of varieties of cytokines or antibody (Dhama *et al.*, 2022). Furthermore, it has been represented. Burberry have potential antioxidant activity as well as anti-inflammatory activity. In a study conducted by Gaurav *et al.* (2020b) reported that berberine not only act as a anti-inflammatory as well as exhibit nephroprotective effect *via* exhibiting antioxidant potential, anti-inflammatory as well as immunomodulatory effect (Gaurav *et al.*, 2020b).

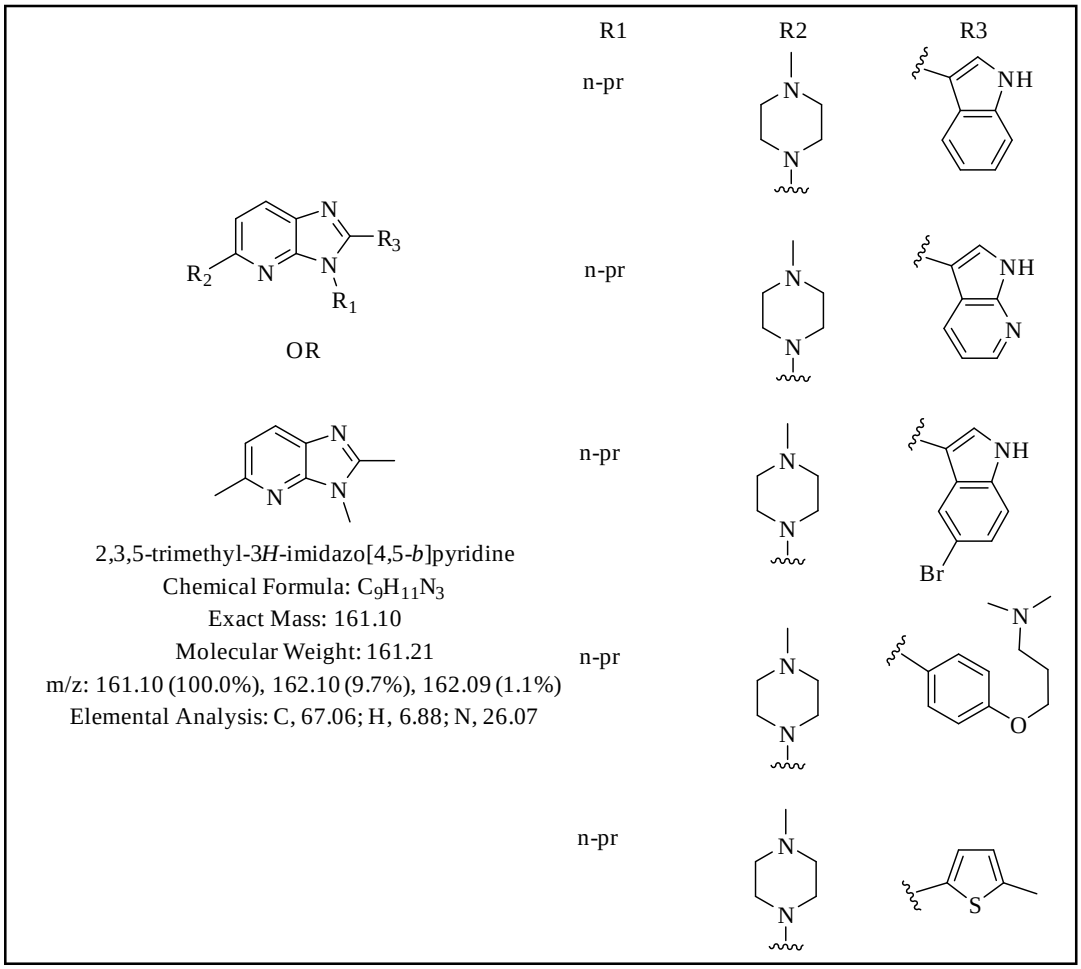


Figure 8: Antifungal benzimidazole derivatives and their chemistry.

2.4.6 Antioxidant activity

A human body is generally subacted by the varieties of free radicals which are produced inside the body due to normal cellular metabolism (Gautam *et al.*, 2021; Venkatachalam *et al.*, 2021). It is also reported that excessive production of the free radicals causes oxidative damage and causes arteriosclerosis, myocardial infarction, diabetes, nephritis, anticancer, *etc.* (Ekbbal *et al.*, 2022; Gaurav *et al.*, 2020b; Gautam *et al.*, 2021). Benzimidazole's protective effect against oxidative damage, generates a new hope for managing oxidative damage and its associated complications. In a study reported by Ates-Alagoz, (2013) reported the effect of retinoidal benzimidazole as an antioxidant and its role in the alleviation of

several disease such asarteriosclerosis, nephritis and carcinogenesis (Ates-Alagoz, 2013). Başaran *et al* evaluated anti-oxidant effect of several synthesised 2-(2-phenyl)-1H-benzo(d)imidazol-1-yl)-N'-(arylmethylene) acetohydrazide derivatives. In the desgined scheme, 12 compounds were synthesised and characterised through NMR, IR and Mass. The antioxidant activity was determined theough on rat liver lipid peroxidation (LPO) levels and microsomal ethoxyresorufin O-deethylase (EROD) activity. The results of the study showed that each synthesized compound exhibited good LPO inhibitory activity (15-57%) excluding compound 6 containinga thiophene ring. Furthermore, it was also reported that each compound exhibited slightly inhibitory activity (2-20%) on EROD (Başaran *et al*., 2020). Palmatine, a naturally occurring bioactive compound exerts potent antioxidant activity *via* redcing oxidative stress. In a reported published by Gaurav *et al*. (2020b) reported antidiabetic and antioxidant activity of palmatine which was found in the polyherbal formulation BGR 34.

2.5 Future perspective

Benzimidazole derivatives has exponential accessibility in therapeutic targets for mitigation of several disease and disorders due to their unique structural activity relationship which contributes to the diversity of the chemical molecules and their biological examinations. Till date, numerous benzimidazoles or their derived derivative accelerated to the major scale for pharmaceuticals and healthcare systems for management of such diseases deals with a lack of therapeutic hope. At the same time, benzimidazole derivatives progressively provide a new hope for sustainable development of healthcare and pharmaceuticals as well as to the nations *via* contributing themselves as anticancer, anti-inflammatory, antifungal, antibacterial, *etc*. Furthermore, it has been reported that benzimidazole compounds in nature such as N-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B12 and helps to increase the utility of Vit-D which helps to cure even manage physiological halts (Gagnon *et al*., 2018; Khan *et al*., 2022b).

Oxidative stress-induced diseases such as myocardial infarction, CVD, nephrotoxicity, cancer, diabetes, are proficiently alleviated by several benzimidazole as oxidative stress is acknowledged as the root cause for induction of varieties of pathogenesis including kidney-associated complications induced by oxidative stress (Gaurav *et al*., 2022; Khan *et al*., 2022a; Yamagami *et al*., 2019). Anastassova *et al*. (2021) enlightens the effect of benzimidazole arylhydrazones as a combined activity for anti-Parkinsonian, neuroprotection and oxidative stress modulation and describebenzimidazole as a potent therapeutic lead for multi-targeted effct in alleviation of the associated complications (Anastassova *et al*., 2021). At present, microbial infection and associated complication is progressively seen in developed and developing countries due to resistance of active pharmaceutical ingredients. The unique SAR of benzimidazoles (Eg. β-lactam antibiotics, macrolides, quinolones, and vancomycin) and their biological assessment leaves new path to overcome the effect of varieties of microorganism strains because of resistance to several antimicrobial agents. Although, derivatives of benzimidazole also contribute as antacids, and in the complications associated with the gastrointestinal. Among several complications associated with the normal function of the body, benzimidazole provides new hope to evade acute and chronic ailments and further development of pharmaceuticals and the healthcare system to promote health and the Nation (Krishnan Janeyulu *et al*., 2014; Özkay *et al*., 2011). The systematic pharmacological role of benzimidazoles against various diseases has been represented in Figure 3.

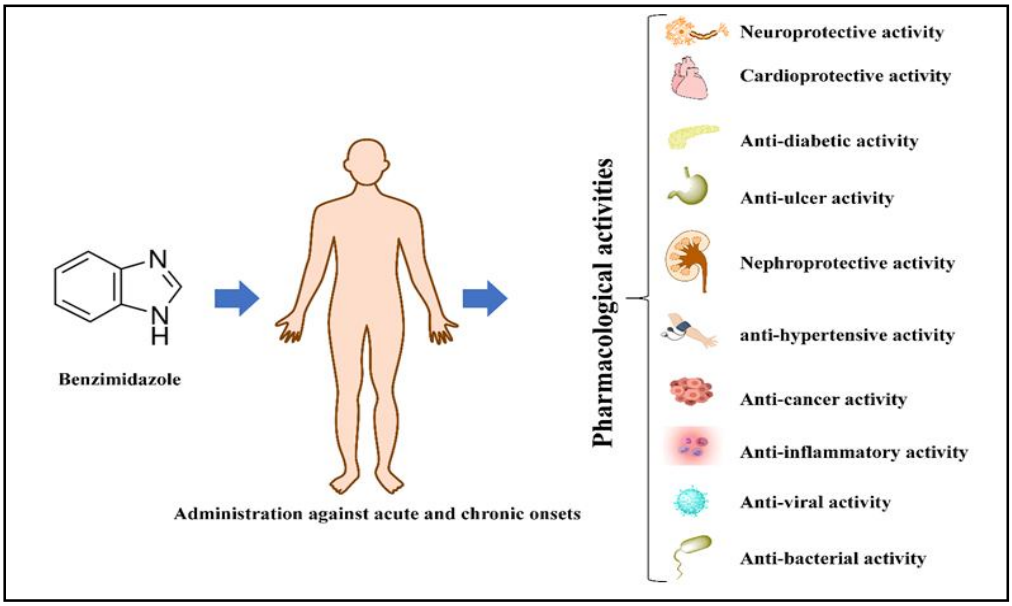


Figure 9: **A graphical representation of benzimidazole pharmacology. The figure represents that benzimidazole exhibits the most effective therapeutic role as neuroprotective, cardioprotective, nephroprotective, antidiabetic, antiulcer, Antihypertension, anti-cancer, anti-inflammatory, antiviral and antibacterial activity. Hence, it can be demonstrated that benzimidazole have wide therapeutic significance in alleviation of several acute and chronic ailments.**

3. Conclusion

The study concludes the multi-mechanistic and therapeutic effect of benzimidazole and their derived derivatives in the alleviation of several acute and chronic ailments associated with the vital organs pathogenasis such as neurodegradation, nephrotoxicity, myocardial infraction, microbial infaction, *etc*. Hence, benzimidazole are contributed as the effective lead for a targeted therapeutic approach for treating disease and maintaining the accessibility of pharmaceuticals and the healthcare system.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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