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Review Article

Pharmacological Effects of Amlaki, Arjuna and Ashoka: A Mini Review

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ABSTRACT

The use of medicinal plants as supplemental or alternative medicine is widespread around the world. For the creation of new drugs, study on these medicinal plants, including pharmacological and toxicological analyses, is crucial. The use of medicinal herbs is seen to be relatively safe because there are rarely any adverse side effects. The significant benefit is that these treatments work in harmony with nature. The usage of herbal remedies is independent of age groups and genders, which is the most important fact. Bangladesh is a country where numerous medicinal plants grow indigenously. Practitioners of alternative medical systems frequently use these plants to treat various ailments. Each plant has a distinct pharmacological action. In this study, we recapitulate the pharmacological activity of Bangladesh's three renowned medicinal plants (Amlaki, Arjuna, and Ashoka). The prominent effects of these plants are summarized in this work. Amlaki shows anticancer and anti-diabetic properties and Arjuna affects the cardiovascular system, pulmonary system, gastrointestinal tract, and different types of inflammation, and Ashoka demonstrates antibacterial, antiulcer, anthelminthic, and anticancer properties. Based on this assessment, a thorough investigation might be carried out to isolate an activity-specific chemical from these plants.

Keyword: Amlaki, Arjuna, Ashoka, Bangladesh

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INTRODUCTION

Historically, medicinal plants have been essential as sources of pharmacological lead compounds. Due to the fact that early humans used plants to heal their illnesses as a result of instinct, taste, and experience, the history of medicinal plants predates that of humans. Long before the prehistoric era, people employed plants for medical purposes. Any plant that has compounds that can be utilized therapeutically or that serve as building blocks for the production of effective pharmaceuticals is considered to be a medicinal plant [1]. Chinese texts, Egyptian papyrus, and ancient Unani scrolls all discussed the use of plants. There is proof that herbal medicine has been used by Unani Hakims, Indian Vaids, and European and Mediterranean cultures for more than 4000 years. Herbs were employed in healing rituals by indigenous cultures in Rome, Egypt, Iran, Africa, and America. Other cultures created traditional medical systems like Unani, Ayurveda, and Chinese Medicine that systematically utilised herbal remedies.

Traditional medical systems are still used extensively on many fronts. The use of plant materials as a source of medicines for a wide range of human maladies has received more attention as a result of factors including population growth, insufficient drug supply, prohibitive cost of treatments, side effects of several synthetic drugs, and the development of resistance to currently used drugs for infectious diseases [2]. Due to the rising costs of maintaining one's own health, herbal treatments have gained popularity in modern society as a means of treating minor illnesses. In fact, there is a significant risk that many medicinal plants could become extinct or lose their genetic variety in the near future due to the market and public demand, which has been so high.

Bangladesh is a country that is situated in a way that allows it to produce large number of plants. Numerous plants possess typical pharmacological properties [3]. Various Bangladeshi rural groups possess innate knowledge of using herbal remedies to treat a variety of ailments. [4]. Different culinary agents used in this country also possess excellent medicinal properties. [5].

In the current study, we evaluated the pharmacological research on three widely used Bangladeshi medicinal plants. This work will researchers to further investigate the underlying mechanism of these plants along with new lead compound development.

Amlaki:

Amlaki (*Phyllanthus emblica*), sometimes referred to as Indian gooseberry, is a popular menage cure that is used in the Indian native medical system to treat a variety of afflictions. Spasmolytic, hypoglycemic, expectorant, purgative, hypolipidemic and hepatoprotective activity have all been linked

to the fruit. According to reports, the *emblica* fruit has antioxidant, antihyperlipidemic, and anti-diabetic components and is a key component of several commercially available hepatoprotective formulations. Fresh *emblica* fruit is used to treat scurvy and pulmonary TB since it has a high ascorbic acid content. Dried fruit is employed as medication for a variety of ailments including alcohol, indigestion, heart difficulties, indigestion, fever, anemia and liver disorders [6].

The majority of the *P. emblica* factory's product is used in India's conventional medication system. The fruits are described as being sweet, sour, acidic, bitter, and pungent by ayurveda. Diabetes can be treated with the help of the fruits. To treat nausea and vomiting, amla greasepaint is combined with red sandalwood (*Pterocarpus santalimun*) and cooked in honey. On irritated eyes, a leaf infusion is used. *P. emblica* fruit's standardized antioxidant component has been utilized as a skin lightener. For chronic diarrhea, the leaves are infused with fenugreek seed. Gonorrhea can be treated with the dinghy's juice, honey, and turmeric. A well-known treatment for a variety of urinary disorders is a decoction made from the fruit and stems of Tinospora cordifolia. In oil painting, the seeds are ground up and used as a helpful treatment for scabies or itching. To slow hair aging, dried fruit was cooked in coconut oil [7].

A) Anti-neoplastic activity:

An *Emblica officinalis* (EO) fruit waterless extract protected mice from the chromosome-damaging effects of the commonly used carcinogen, 4-benzo pyrene. According to results of another investigation, *P. emblica* greatly lowers convinced solid excrescences, which suggests a possible connection to cell-cycle control. In mice displaying excrescences, the anti-tumor activity of a *P. emblica* waterless fruit extract resulted in a 35-percent increase in life duration. It has been studied how dehydrated amla greasepaint affects the regulation of antioxidative enzymes and toxicity in rats exposed to the chemical carcinogen dimethyl hydrazine. The chemo-preventative effects of emblica against DMBA confirmed genotoxicity in Swiss albino mice are veritably well shown [8].

B) Hepato-protective activity:

Scientist attempted to assemble phytochemical, botanical and pharmacological data on *P. emblica*, a medicinal condiment utilized in the Indian system of medicine. This condiment was intended to be used most often by diabetics and others with liver complaints as a hepatoprotective agent. This condiment also exerted significant neuroprotective, anticancer, antidiarrheal and anti-cholesterol effects. It would be useful to comprehend this significant herbal medication to conduct future research on the insulating and identify

other bioactive compounds from the extract of emblica fruit [9].

C) Hypoglycemic activity:

Several recent research published in the literature have demonstrated that amla can efficiently lower the blood glucose level through gluconeogenesis and glycogenolysis inhibition. When given orally to diabetic mice at intervals of 0, 1, or 2 hours, a waterless *P. emblica* fruit extract (200 mg/ kgb.w.) considerably lowered the blood glucose level. In diabetic rats, it was also shown that the hypoglycemic impact of ethanolic extracts (100 mg/ kgb.w) of amla seeds considerably decreased the blood sugar status within 4 hours [10].

Arjuna

Arjuna, commonly referred to as the "Arjun tree," is a tree that is widely planted in India. It has vibrant medicinal packages such as anti-inflammatory, antibacterial, and antioxidant.

Heart issues are less likely to occur thanks to Arjuna. It aids in the heart's normal operation by toning and strengthening the cardiac muscles. Strong anti-hypertensive properties of the arjuna tree also help lower excessive blood pressure [11].

Arjuna has a number of advantages. They're provided here with a scientific perspective-

1) Arjuna's treatment of angina

Arjuna is helpful in the treatment pain (angina). According to studies, the boat of Arjuna significantly lessens the agony of death by reducing the level of the stress hormone cortisol. Arjuna also enhances HDL conditions, lowers blood pressure in humans, and boosts exercise tolerance with stable angina.

2) Arjuna for Diarrhea

Arjuna might be helpful for treating diarrhea. Arjuna has several compounds that are both acidic and antibacterial. Additionally, it possesses antibacterial properties that prevent intestinal infections brought on by microbes. It controls gastrointestinal motility and stops excessive electrolyte and water loss from the body.

3) Arjuna for Heart Complaint

Arjuna works as a cardiotonic and strengthens the heart muscles, making it potentially beneficial in treating cardiac ailments. Similar to the tannins and glycosides found in Arjuna boat, some components have an antioxidant effect that guards the heart muscles and blood vessels from harm from free radicals. In order to improve blood flow, Arjuna dissolves the shrine and aids in the dilation of the blood vessels. So it works well to treat cardiac issues including excessive blood pressure, pulsations, and rapid-fire twinkling [12].

4) Arjuna for Airway Inflammation (bronchitis)

Arjuna is effective for treating lung conditions such bronchitis, asthma, and coughing. According to Ayurveda, poor digestion is the root cause of lung conditions

like bronchitis, which are referred to as Kasroga. Ama's conformation is caused by a poor diet and insufficient waste removal (poisonous remains in the body due to indecorous digestion). This Ama builds up in the lungs as mucus, which causes bronchitis. Because Arjuna balances Kapha, it aids in reducing Ama and removing mucus [13]

5) Arjuna's heart rate drops

According to studies, the Arjuna Dinghy extract may cause Bradycardia, or a dramatic decrease in heart rate. Therefore, if you have low blood pressure or a slow heartbeat, it is recommended that you speak with your doctor before using Arjuna.

The Arjuna dinghy (chaal) is designed to help with high cholesterol management. owing to its potent anti-inflammatory and antioxidant properties. It decreases the levels of triglycerides, bad cholesterol (LDL), and total blood cholesterol. Consequently, it helps to improve the status of good cholesterol [14].

The Arjuna boat may be helpful in treating earaches brought on by various infections. It has an anti-microbial effect that stops microorganisms from spreading and infecting people. Additionally, it contains anti-inflammatory activity that lessens the discomfort that is related to it [15]. Arjuna greasepaint's immunomodulatory effects may aid to strengthen the weak system. By varying the number of antibodies, it modifies how the susceptible system reacts. Consequently, it strengthens the weak system. Due to its expectorant activity, arjuna is regarded as being beneficial for coughing. It alleviates coughing by encouraging the stashing of foam by the lungs' air passageways. The Arjuna dinghy extract (Arjuna chaal) delays the aging of the skin. A rise in the proportion of free revolutionaries is correlated with aging. Arjuna contains potent antioxidant properties that guard against skin damage brought on by these free radicals. It improves skin cells, moisturizes the skin, and aids in the construction of new skin cells. Additionally, it stops the skin from thinning and drooping [16].

Ashoka:

The Ashoka tree produces rain-timber. Its former range included the western shoreline of the Indian key, the middle sector of the Western Ghats, and the central regions of the Deccan table. Ashokas are renowned for their lovely foliage and delicious blossoms. It's a charming little tall evergreen tree with lush clusters of deep green foliage. Ashoka assists women in managing a variety of gynecological and menstrual issues, including as painful, irregular, and heavy periods. To relieve belly discomfort and spasms, it can be taken twice day after reflections in the type of churna, greasepaint, or capsules. Because Ashoka dinghy juice and kwath have blood cleansing properties, they can help enhance good skin [17].

Due to its Kasaya (tangy) quality, Ashoka is said to be helpful in stopping internal bleeding, particularly in the case of piles. Due to its Ropan (mending) characteristic, it is also beneficial in quickly reducing pain and healing wounds. On get rid of oily and dull skin, apply Ashoka flower juice or kwath to the skin. The discomfort or cramps that occur during or just before a menstruation are known as dysmenorrhea. This ailment is referred to as Kasht-aartava in Ayurveda. According to Ayurveda, Vata dosha controls and regulates Aartava, or menstruation. Vata must thus be under control in a woman in order to treat dysmenorrhea. Ashoka has the ability to balance Vata and provides relief from dysmenorrhea. It soothes overactive Vata and lessens cramping and discomfort throughout the menstrual period [18].

A) Use as antibacterial agents:

Saraca indica extract's flowers and flowerings were noted to exert antibacterial pressure on enterobacteria. Or The minimum Restrictive attention (MIC) approach was used to assess if water-answerable pieces inhibited bacterial growth. Methanolic, waterless extracts, ethanolic and acetone have been shown to have antibacterial properties in several literature papers. Dinghy, withered flower children, and *S. asoka's* leaves [19].

B) Anti-diarrheal effects:

Ashoka exerts strong anti-diarrheal effects. Alkaloids, flavonoids, and tannins all contribute to this. They function by preventing bowel motions and preserving the body's water balance. The flavonoids in Ashoka also help by lowering the molecules that cause diarrhea-related discomfort and annoyance [20].

C) Antiulcer activity:

The antiulcer activity is present in the Saraca indica production. It has been demonstrated that the waterless aqueous extract of leaves, dried flower buds, stems, and seeds causes ulcers in albino mice. *Saraca indica* flower suspense demonstrates an implicit antiulcer exertion through at least one or more media, such as intrinsic gastric mucosal prostaglandin conflation, mucus stashing stimulation, and suppression of rudimentary gastric stashing [21].

D) Antitumor activity:

Ashoka possesses anti-tumor activity. This is as a result of flavonoids being present in it. When it comes to skin cancer, an enzyme that promotes the formation of excrescences is inhibited by flavonoids. Additionally, it lessens the risk of skin cancer relapsing.

The health advantages of Ashoka greasepaint are many. It aids in controlling issues with periods (ages), such as irregular ages, stomach ache, cramps, etc. It functions as a uterine alcoholic and controls hormones and menstrual inflow. It possesses properties that are antibacterial, anti-inflammatory, and

analgesic, which aid in the treatment of infections, swelling, and pain. Because of its antioxidant activity, Ashoka greasepaint aids in the management of skin-related issues and helps to maintain smoother skin by eliminating toxins from the body. Due to the existence of certain chemical composites, it also aids in treating conditions like ulcers, infection, fever, cancer, diabetes, piles etc. [22].

Conclusion:

We are going further away from nature as our way of life becomes more technologically advanced. Despite the fact that we are a part of nature, we cannot escape it. Herbs are natural items; thus, they have no negative side effects and are also relatively safe, environmentally friendly, and locally accessible. Many plants are traditionally used to treat illnesses associated with certain seasons. To save lives of people, they must be promoted. Many commonly used medicinal plants, with a few notable exceptions, have not undergone the thorough plant physiological characterization that food crops or model plant systems have. In general, many mechanisms for the biosynthesis of certain medicinal substances and the factors (biotic and abiotic) influencing their production remain obscure, even though active phytochemicals may have been found. The plant constituents must be studied well to nullify the effects of toxic substances. To counteract the effects of harmful compounds, the plant's contents must be thoroughly investigated.

References

1. Sofowora A, Ogunbodede E, Onayade A. The role and place of medicinal plants in the strategies for disease prevention. African journal of traditional, complementary and alternative medicines. 2013;10(5):210-29.

2. Chen SL, Yu H, Luo HM, Wu Q, Li CF, Steinmetz A. Conservation and sustainable use of medicinal plants: problems, progress, and prospects. Chinese medicine. 2016;11(1):1-0.

3. Hasan M, Islam MM, Shorna MJ, Sarder MR. Plant antimicrobial peptides in Bangladesh: sources, extraction, purification and characterization. Jagannath University Journal of Life and Earth Science. 2021; 6(1): 95-110.

4. Rahman MA, Uddin SB, Wilcock CC. Medicinal plants used by Chakma tribe in Hill Tracts districts of Bangladesh. Indian J. Traditional Knowledge. 2007; 6(3):508-517.

5. Islam MM, Manik MIN, Zobayed A, Noor F. A review on medicinal properties some commonly used culinary agents of Bangladesh. J Med Plants Stud. 2021;9(3):111-117.

6. Nizamuddin M, Hoffman J, Larm O. Fractionation and characterization of carbohydrates from Emblica officinalis G.fruit. Swed. J. Agric. Res. 1982;12(1): 3-7.

7. Barthakur NN, Arnold NP. Chemical analysis of the emblic (Phyllanthus emblica L.) and its potential as a food source. Scientia Horticulturae. 1991;47(1-2):99-105.

8. Anila L, Vijayalakshmi N. Flavonoids from Emblica officinalis and Mangifera indica—effectiveness for dyslipidemia. Journal of Ethnopharmacology. 2002;79(1):81-7.

9. Gulati RK , Agarwal S, Agrawal SS. Hepatoprotective studies on Phyllanthus emblica Linn, and quercetin. Indian J Exp Biol.2015; 33(4):261-8.

10. Sultana S, Ahmed S, Sharma S, Jahangir T. Emblica officinalis reverses thioacetamide-induced oxidative stress and early promotional events of primary hepatocarcinogenesis. The Journal of pharmacy and pharmacology. 2004;56(12):1573–1579.

11. Rajni HS, Manish RA. Review on pharmacological Ayurvedic compound of Terminalia arjuna. International journal of phytotherapy research. 2014;4(4):31-8.

12. Dwivedi S, Chopra D. Revisiting Terminalia arjuna–an ancient cardiovascular drug. Journal of traditional and complementary medicine. 2014;4(4):224-31.

13. Amalraj A, Gopi S. Medicinal properties of Terminalia arjuna (Roxb.) Wight & Arn.: a review. Journal of traditional and complementary medicine. 2017;7(1):65-78.

14. Gaherwal S, Anare R, Wast N, Prakash MM. Immunomodulatory efficacy of Terminalia arjuna against Aspicularis tetraptera in mice. International Journal of Microbiological Research (IJMR). 2014;5(1):23-9.

15. Das K, Chakraborty PP, Ghosh D, Nandi DK. Protective effect of aqueous extract of Terminalia arjuna against dehydrating induced oxidative stress and uremia in male rat. Iranian Journal of Pharmaceutical Research: IJPR. 2010;9(2):153.

16. Gupta S, Bishnoi JP, Kumar N, Kumar H, Nidheesh T. Terminalia arjuna (Roxb.) Wight & Arn.: Competent source of bioactive components in functional food and drugs. The Pharma Innovation Journal. 2018;7(3):223-31.

17. Borokar AA, Pansare TA. Plant profile, phytochemistry and pharmacology of Ashoka (Saraca asoca (Roxb.), De. Wilde)-A comprehensive review. Int. J. Ayurvedic Herb. Med. 2017;7(2):2524-41.

18. Bhalerao SA, Verma DR, Didwana VS, Teli NC. Saraca asoca (Roxb.), de. Wild: an overview. Annals of plant sciences. 2014;3(7):770-5.

19. Tabassum N, Hamdani M. Plants used to treat skin diseases. Pharmacognosy reviews. 2014;8(15):52-60.

20. Asoka BV. Herbal boon to gynecological problems-an overview of current research. Ayurveda J Health. 2014;12(4):58-62.

21. Shah A, Krishnamurthy R. Swine flu and its herbal remedies. Int J Eng Sci. 2013;2(5):68-78.

22. Mishra A, Kumar A, Rajbhar N, Kumar A. Phytochemical and pharmacological importance of Saraca indica. Int. J. Pharm. Chem. Sci. 2013;2(2):1009-13.

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Review Article

Evaluation of Anti-fungal Agent (KETOCONAZOLE) and It's convenient delivery system

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ABSTRACT

An antifungal medication, also known as an antimycotic medication, is a pharmaceutical fungicide or fungistatic used to treat and prevent mycosis such as athlete's foot, ringworm, candidiasis (thrush), serious systemic infections such as cryptococcal meningitis, and others. Such drugs are usually obtained by a doctor's prescription, but a few are available over the counter (OTC) (Wikipedia.com). Azoles are commonly used antifungal agents. Azole antifungals act through selectively inhibiting the synthesis of fungal cell ergosterol, and they alter the permeability of cell membrane by binding with the phospholipids in the fungal cell membrane. The azole antifungal drugs used in the treatment composed of either two or three nitrogens in the azole ring and are thereby classified as imidazoles (e.g., ketoconazole and miconazole, clotrimazole) or triazoles (e.g., itraconazole and fluconazole), respectively. In this review article, we have tried to evaluate ketoconazole and it's convenient delivery system. Ketoconazole is mostly effective in oral drug delivery system but because of it's some serious adverse effect it is forbidden in many countries from taking orally. It is also very low soluble in orally. If we compare oral and topical drug delivery system, then topical is always preferable because of it's high solubility. Ketoconazole is a broad spectrum, systemic antifungal agent. Lipid vesicular systems including conventional liposomes, ethosomes, deformable liposomes, and ethanol containing deformable liposomes were prepared as nanocarriers for ketoconazole, respectively. Characterization of the vesicles was based on particle size, zeta potential, entrapment efficiency, and transmission electron microscopy. The results demonstrated that ethanol-containing deformable liposomes improved both in vitro and in vivo skin deposition of ketoconazole. Microemulsion formulations of ketoconazole enhanced percutaneous absorption of the drug, and it has been

shown that a microemulsion and cyclodextrin combination enhanced the antifungal activity of the drug in vitro against Candida parapsilosis test. This article is made upon the basis of some researches regarding the topic. We have also discuss about dry granulation technology and SLN system according to some researches for making oral route convenient. There is also a short discussion over topical drug delivery system.

Keywords: Anti-fungal, azoles, ketoconazole, microemulsion, parapsilosis , etc.

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INTRODUCTION

Ketoconazole is an antifungal drug which is used to treat skin infections caused by a fungus (yeast). It can also prevent them coming back. It treats different types of fungal infections including: athlete's foot, jock itch, an infection in the groin area, sweat rash (intertrigo), a rash that usually appears in folds of skin, dandruff seborrhoeic dermatitis, where our scalp or other areas of our skin become scaly and dry or grease, pityriasis versicolor, sometimes called tinea versicolour, where small patches of skin become scaly and change color etc. Ketoconazole has approval for use in the treatment of fungal infections of the skin and systemic fungal infections. These include blastomycosis, histoplasmosis, paracoccidioido- mycosis, coccidioidomycosis, and chromomycosis. The most common use of ketoconazole for skin infections is that of tinea versicolor. Ketoconazole is typically not the first-line medication anymore, because of it's some dangerous adverse effects on liver when taken orally. Ketoconazole works as an antifungal agent by inhibiting the cytochrome P450 14α-demethylase enzyme. This enzyme is responsible for inhibiting the biosynthesis of triglycerides and phospholipids by fungi. Ketoconazole can be found in different dosage forms and they are oral tablet, topical cream, topical foam, shampoo, and topical gel. The most effective dosage form is oral tablet. But it is not allowed to act as first line treatment when it is taken orally as tablet dosage form. The most widely used form is cream in topically. Tablets are popular dosage form as for patient convenience, good stability, easy and low-cost manufacturing (Taneri et al., 2010; Gohel & Jogani, 2005). Tablet should possess certain properties in accordance with specifications required, i.e. tablet hardness, friability, disintegration time and dissolution (Edge et al., 2002). The comparison with other azole group like: fluconazole, itraconazole, voriconazole etc are less effective than ketoconazole. Ketoconazole has very low solubility effect, but high has high permeation. Though it has some serious adverse effects, there are so many researches to overcome those problems. In this review article, we have tried to describe all about ketoconazole briefly.

History of ketoconazole:

In the history of discoveries of fungal pathogens, the nineteenth century has witnessed two important events. The causal

organism of a silkworm disease, muscardine, a fungus named later as Beauveria bassiana, was revealed by agostino Bassi in 1835. Six years later, in 1841, the causal agent of the human scalp disease, favus, being a fungus was discovered by David Gruby. The Gruby's unique and innovative method for the isolation of fungus from the infected scalp and on potato slices, repeated infection of the healthy tissues by the isolated fungus (parallel to the Koch's postulate) was left ignored in the pages of science history due to reasons not related to science. The fact remains that even after the seminal researches by Bassi and Gruby, The knowledge of the fungal diseases remained much less than that of bacterial diseases. Compared to bacterial diseases (among which some of them were epidemic) of human beings, diseases caused by fungi were not epidemic in nature and often are occasional but consequences of some mycoses that can be severe to lethal. To treat fungus antifungal agent from azole group are discovered. Ketoconazole was discovered in 1976 and released in the early 1980s, and was one of the first available oral treatment for fungal infections (griseofulvin was available before ketoconazole). In 1979, ketoconazole (Bossche 1997), a second generation drug containing imidazole group, was found to be suitable to treat fungal infections of the skin such as athlete's foot, jock itch, ringworm, and seborrhoea (dry, flaking skin) and is available as a cream, gel, and shampoo.

Mechanism of Action of ketoconazole:

Ketoconazole blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14alpha-demethylase responsible for the conversion of lanosterol to ergosterol in the fungal cell membrane. This results in an accumulation of methylated sterol precursors and a depletion of ergosterol within the cell membrane thus weakening the structure and function of the fungal cell membrane (NIH; DailyMed. Current Medication Information for Nizoral (Ketoconazole) Tablet .

Drawbacks of ketoconazole:

Some of the drawbacks associated with the ketoconazole are

(i) limited efficacy against Aspergillu
(ii) metabolically vulnerable (<5 % excreted unchanged),
(iii) 95–99 % of drug bound to lipoproteins in serum (activity drops 10–1,000-fold in the presence of serum with in vitro tests),
(iv) poor penetration into CSF, and
(v) best absorbed by the gut in acid conditions, so antacids should not be prescribed at the same time as ketoconazole.

Different dosage forms of Ketoconazole:

Name of the antifungal Agent	Conventional dosage forms	Nano based delivery technology	References
Ketoconazole	Cream Gel Foam Shampoo Tablet	Liposome Ethosome Transfersome Microemulsion Microemulsion	Patel et al.(2011) Che et al. (2015) Guo et al. (2015) Guo et al. (2015) Guo et al. (2015)

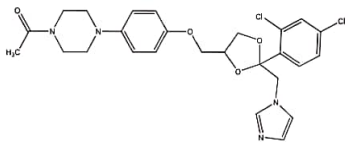
Fungal strains of ketoconazole :

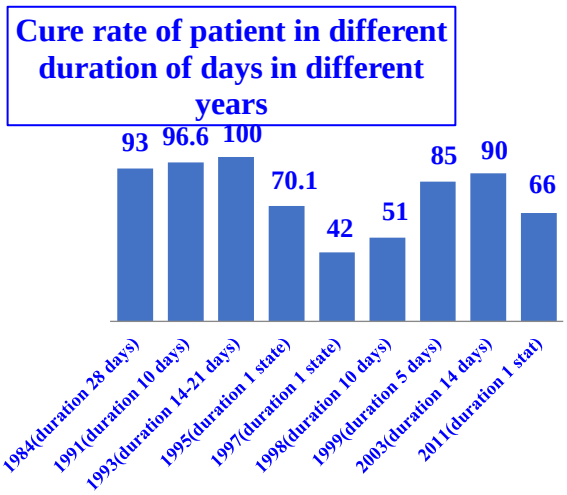
Toxicity of ketoconazole :

Ketoconazole is much less toxic than Amphotericin B. It is less effective and more toxic than newer azoles. Ketoconazole interferes With the biosynthesis of adrenal and hormones producing significant endo-Crine effects, such as gynaecomastia, infertility,And menstrual irregularities. This effect is less With flucanozole, itraconazole, and voriconazole. Gastric upset is seen with all orally used azoles. Hepatic impairment occurs with ketoconazole. there is asymptomatic increase in serum Transaminases (Foster et al. 1981). (book: Recent Trends in Antifungal Agents and Antifungal Therapy: page no. 223) Symptoms of overdose include acute liver injury, which may include both hepatocellular and cholestatic injury, accompanied by anorexia, fatigue, nausea and jaundice (https://pubchem.ncbi.nlm.nih.gov/compound/Ketoconazole#section=Toxicity&fullscreen=true).

Most convenient route for ketoconazole

Topical route is more convenient than oral, because in topical route ketoconazole shows less adverse effect than oral. Oral ketoconazole goes through systemic circulation. ketoconazole is an antimycotic agent exhibiting unselective inhibition toward CYP17, CYP11B1, CYP11B2, CYP11A1. Oral ketoconazole interact with other drug where topical route doesn't interact, it just absorb into the skin surface and doesn't go through systemic circulation (https://www.sciencedirect.com/topics/neuroscience/ketoconazole#:~:text=Because%20of%20its%20erratic%20absorption,severe%20infections%20in%20immunocompromised%20patients%20%E2%80%A6

Compound	Fungal strains & MIC (µg/ml)
Ketoconazole 	*C. albicans (0.03-0.25)* *C. parapsilosis (0.03-0.06)* *C. tropicalis (0.03-4)* *C. krusei (0.03)* *C. guilliermondii (0.5-4)* *C. glabrata (0.03-2)*



From the above graph, we can know the cure rate of patients when ketoconazole drug was given topically. In 1986, the cure rate was 84% when the duration was 11-22 days and the dosage form was cream based form, but in 2011 it decreased very rapidly turned into

34% when it was applied as a soap and the duration was 30 days.

So, we can easily say that, there was always an ups and down of ketoconazole drug's cure rate with the changes of dosage forms and duration, whether it was given orally or topically. In average, topical route for ketoconazole is quite better than oral.

Why topical route is more convenient:

Uses of ketoconazole on a skin is more convenient, because skin absorbs medicine only into the surface it doesn't go through the systemic circulation, so it can't interact with other drugs and no first pass metabolism is occur. Topical route shows less adverse effect. Even in pregnancy and breastfeeding Ketoconazole cream or shampoo can be used. Only tiny amounts are absorbed into our body so it will not affect the baby. If any mother is using ketoconazole on her breast and she want to breast feed her child, she just need to wash her breasts and nipples and then wash her hands before feeding her baby.

Why oral route is not convenient:

The major drawback in the therapeutic application and efficacy of ketoconazole as an oral dosage form has been its very low Aqueous solubility (0.017 mg/mL) because of its hydrophobic Structure (Connors & Elder, 2004; Van der Meer et al., 1980).The low solubility across the physiological pH range of ketoconazole is reported to result in erratic and variable absorption from the gastrointestinal (GI) tract, hence not recommended For use in treating life-threatening fungal infections (Levine,1982). Ketoconazole is not first line treatment and it interact with other drugs which is not convenient. The drugs whom ketoconazole interacts with are given below

- omeprazole,
- lanosprazole
- sucralfate
- Digoxin,
- Coumarin
- Mefloquine
- Aspir 81 (aspirin)
- Aspirin Low Strength (aspirin)
- Benadryl (diphenhydramine)
- Cymbalta (duloxetine)
- Fish Oil (omega-3 polyunsaturated fatty acids)
- Flonase (fluticasone nasal)
- Lipitor (atorvastatin)
- Lyrica (pregabalin)
- Metoprolol Succinate ER (metoprolol)
- MiraLAX (polyethylene glycol 3350)
- Paracetamol (acetaminophen)
- ProAir HFA (albuterol)
- Singulair (montelukast)
- Synthroid (levothyroxine)
- Tylenol (acetaminophen)
- Vitamin B12 (cyanocobalamin)
- Vitamin D3 (cholecalciferol)
- Zyrtec (cetirizine)

(https://pubchem.ncbi.nlm.nih.gov/compound/Ketoconazole#section=Interactions&fullscreen=true

https://www.researchgate.net/publication/286195982

https://www.drugs.com/drug-interactions/ketoconazole.html)

Comparison between different azoles:

Azole	Effect of dose	Biological half life	Absorption rate	Rae of elimination	Clearance	
Ketoconazole	A single 200 mg oral dose produces a Cmax of 2.5-3 mcg/mL with a Tmax of 1-4 h.	Ketoconazole experiences biphasic elimination with the first phase having a half-life of 2 hours and a terminal half life of 8 hours	At pH values above 3 it becomes increasingly insoluble with about 10% entering solution in 1 h. At pH less than 3 dissolution is 85% complete in 5 min and entirely complete within 30 min	Only 2-4% of the ketoconazole dose is eliminated unchanged in the urine. Over 95% is eliminated through hepatic metabolis	Ketoconazole has an estimated clearance of 8.66 L/h.	
Fluconazole	Steady-state concentrations are achieved within 5 to 10 days after oral doses of 50-400 mg administered once daily.	The terminal elimination half-life in the plasma is approximately 30 hours (range: 20-50 hours) after oral administration.	In healthy volunteers, the bioavailability of orally administered fluconazole is measured to be above 90%	A study of a 50mg radiolabeled dose of fluconazole revealed that 93.3% of the dose was found excreted in the urine.	One clinical study of healthy subjects showed total clearance of 19.5 ± 4.7 mL/min and renal clearance of 14.7 ± 3.7 mL/min (1.17 ± 0.28 and 0.88 ± 0.22 L/h).	
Itraconazole	Loading dose: 200 mg orally 3 times a day for the first 3 days of therapy Maintenance dose: 200 mg orally once a day	After a single oral dose, the terminal elimination half-life of itraconazole is about 24 hours.	The absolute oral bioavailability of itraconazole is 55%, and is maximal when taken with a full meal.	Fecal excretion of the parent drug varies between 3-18% of the dose. Renal excretion of the parent drug is less than 0.03%	381 +/- 95 mL/minute [IV administration]	

				of the dose. About 40% of the dose is excreted as inactive metabolites in the urine.		
Voriconazole	Loading Dose: 6 mg/kg IV every 12 hours for the first 24 hours	The elimination half-life of voriconazole is approximately 6 hours	The oral bioavailability Is estimated to be 96% in healthy adults.	Voriconazole is eliminated via hepatic metabolism with less than 2% of the dose excreted unchanged in the urine.	The clearance of voriconazole is estimated to be a mean of 5.25-7 L/h in healthy adults for the linear portion of the drug's kinetics.	

From the above table we can easily say that the absorption rate, elimination rate, clearance and biological half life are greater in ketoconazole than itraconazole and flucoazole, but the absorption rate of the voriconazole is greater than the ketoconazole.

How to make tablet dosage form of ketoconazole convenient?

Ketoconazole is extremely hydrophobic with high molecular weight that leads to poor flowability and difficulty during compaction (Jacobs et Al., 2016; Molaei et al., 2018). Suitable manufacturing process for this kind of drug is wet Granulation technique so it can be compacted into a good tablet (Consiglieri et al., 2010; Javaheri et al., 2014). By wet granulation technique, the resulting tablet shows a change in color, indicating Instability issue due to photochemical reaction that become prominent after solvent exposure (Mhaske & Sahasrabudhe, 2011; staub et.al. 2010). The major drawback in the therapeutic application and efficacy of ketoconazole as an oral dosage form has been its very low aqueous solubility (0.017 mg/mL) because of its hydrophobic structure (Connors & Elder, 2004; Van der Meer et al., 1980). On the basis of its solubility across physiologically relevant pH conditions and absorption characteristics, ketoconazole is classified in the Biopharmaceutics Classification system (BCS) as a class II drug. There are some researches for making ketoconazole tablet more convenient without any kind of adverse effects or less adverse effects. We have summarizes those researches through pointing below and there is also a graph which shows the more relevant research for making tablet dosage form of ketoconazole more convenient.

1) By changing granulation technique:

To overcome the stability problem and to improve flowability, there is a research which introduce dry granulation technique in formulation of ketoconazole tablet (Pertanika Journal of science and technology – July 2020). On that research paper, dry granulation technique was applied with spray dried lactose (SDL) and Avicel® PH-102 were used as filler binder excipient in combination and sodium starch glycolate

(SSG) was used as disintegration agent in the formulation of ketoconazole tablet.

AN IDEAL KETOCONAZOLE TABLET REQUIREMENTS

1)HARDNESS	Tablet hardness of all formulation fell in value between 4.6 to 5.0 Kp that within range of acceptable value (Fatmawati et.al. 2017).
2) FRIABILITY	The Friability of ketoconazole tablets were mostly below 1% and met specification required (Winarti et.al 2017).
3) DISSOLUTION RATE	According to the compendium ketoconazole in tablet dosage form is required to dissolve not less than 80% in the thirty minutes (Ministry of health, 2014).
4) DISINTEGRATION TIME	A tablet disintegration should complete within fifteen minutes (Schmidt & Löbenberg, 2010).

Ketoconazole tablets were formulated according to factorial design 2^2 with two factors, those are filler combination and disintegration agent, in two levels of concentration. Filler combination consisted of SDL and Avicel® PH-102 in weight ratio of 2:1 and 4:1 as the level difference. SSG was used as disintegration agent with two concentrations of 2 and 4%. API composition in each tablet was equal to 200 mg of ketoconazole. The formulation which contained high level of filler combination and low level of disintegration agent is complied with the requirement.

2) By using SLNs (Solid Lipid Nanoparticles)

KTZ is a chemically imidazole-based antifungal drug with limited water solubility (0.04

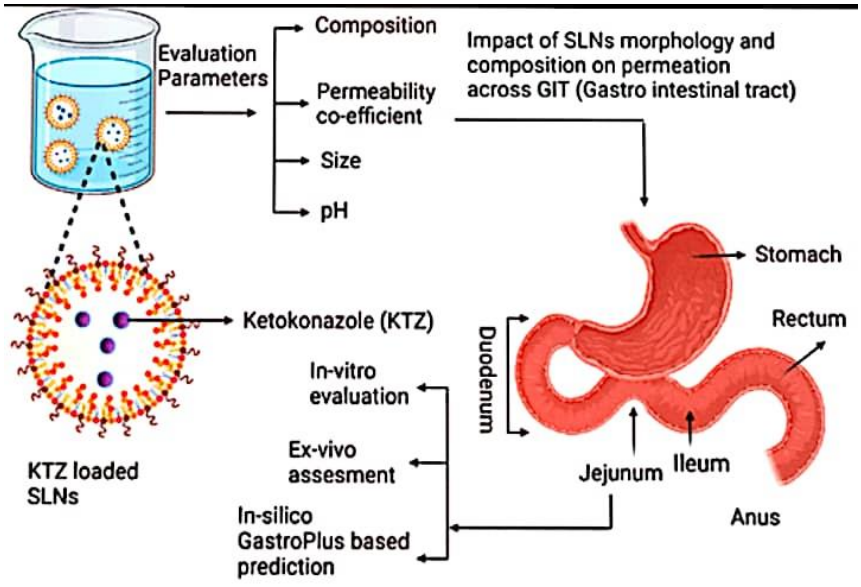
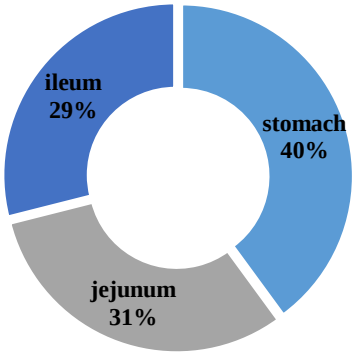


Fig: from ACS Omega 2022, 7, 22406−22420

mg/mL), dermal irritation (free drug), and short elimination half-life (3.3 h). SLNs have been well explored for oral delivery of various poorly soluble drugs in the literature using biocompatible lipid, surfactant, and stabilizer. These SLNs offer convincing benefits as drug delivery carriers, such as drug solubilization, stability, controlled size, improved oral absorption, and augmented therapeutic effectiveness (ACS Omega 2022, 7, 22406−22420). The optimized KTZ loaded SLN formulation was characterized for particle size, zeta potential, solid-state properties, in vitro/ex vivo (rat skin and human dermatome skin), and in vivo pharmacokinetics in the rat model. The long-term stability study at different temperatures and photostability ensured the success of the product over a period of one year. (ACS Omega 2022, 7, 22406−22420). Ex vivo findings suggested pH, composition, size, and permeability coefficient-dependent permeation of SLNs across the stomach, jejunum, and ileum. Confocal laser scanning microscopy (CLSM) confirmed a relatively high degree of penetration of the optimized formulation K-SLN (66.1% across the stomach, 51.5% across the jejunum, and 47.9% across the ileum) as compared to KSUS (corresponding values of 21.7%, 18.2%, and 17.4%)(ACS Omega 2022, 7, 22406−22420).

Degree of penetration of ketoconazole while using with SLN with certain conditions



In K-SLN, the compositions of the CATO 2%, tween 80 1.4%, PEG600 1.5%, PL90 0.06% and KTZ 0.6% are more effective than any other composition. The approach is promising for enhanced oral absorption from the distal region of the GIT for reduced intestinal side effects and more systemic access (ACS Omega 2022, 7, 22406−22420)

Conclusion:

Ketoconazole is such kind of antifungal agent, which is more effective in oral route than topical, but because of it's dangerous adverse effect it is less used in orally. Topical route has less adverse effects for ketoconazole drug, but because of It's slow penetration through skin it is less effective when applied topically. Recently, there are so many researches over oral administration of

ketoconazole drug to make it more effective with less adverse effects. There are two ways to make oral route convenient for ketoconazole, one is by using dry granulation technique and another is by using SLNs (Solid lipid nanoparticles). From these two techniques, SLNs are preferred most. So, we can easily say that, for now skin is more convenient route for ketoconazole drug, but it is not too far that one day oral route will be recognize as most convenient route for ketoconazole.

References:

Features	References
Abstract	**1)** Wikipedia.com **2)** book: Recent Trends in Antifungal Agents and Antifungal Therapy: Thompson et al. 2009 **3)** Guo et al. 2015 **4)** Che et al. 2015; Patel et al. 2011
Introduction	**1)** Taneri et al., 2010; Gohel & Jogani, 2005 **2)** Edge et al., 2002
History of ketoconazole	**1)** Bossche 1997
Mechanism of Action of ketoconazole	**1)** Van Tyle JH. Ketoconazole. Mechanism of action, spectrum of activity, pharmacokinetics, drug interactions, adverse reactions and therapeutic use. Pharmacotherapy. 1984 Nov-Dec;4(6):343-73. [PubMed] **2)** Hu Z, He B, Ma L, Sun Y, Niu Y, Zeng B. Recent Advances in Ergosterol Biosynthesis and Regulation Mechanisms in *Saccharomyces cerevisiae*. Indian J Microbiol. 2017 Sep;57(3):270-277. [PMC free article] [PubMed]
Drawbacks of ketoconazole	**1)** book: Recent Trends in Antifungal Agents and Antifungal Therapy: page no. 195
Different dosage forms of Ketoconazole	**1)** book: Recent Trends in Antifungal Agents and Antifungal Therapy: page no. 178
Fungal strains of ketoconazole	**1)** book: Recent Trends in Antifungal Agents and Antifungal Therapy: page no. 201 **2)** Meerpoel et al. (2010)
Toxicity of ketoconazole	**1)** https://pubchem.ncbi.nlm.nih.gov/compound/Ketoconazole#section=Toxicity-&fullscreen=true
Most convenient route of administration for ketoconazole	1) https://www.sciencedirect.com/topics/neuroscience/ketoconazole#:~:text=Because%20of%20its%20erratic%20absorption,severe%20infections%20in%20immun-ocompromised%20patients%20%E2%80%A6
Why topical route is more convenient?	**1)** https://www.nhs.uk/medicines/ketoconazol**e/**
Why oral route is not convenient?	**1)** https://pubchem.ncbi.nlm.nih.gov/compound/Ketoconazole#section=Interactions&fullscreen=true **2)** https://www.researchgate.net/publication/286195982

	3) https://www.drugs.com/drug-interactions/ketoconazole.html
Comparison between different azoles	**1)** https://www.ncbi.nlm.nih.gov
How to make tablet dosage form of ketoconazole?	**1)** ACS Omega 2022, 7, 22406−22420: Jacobs et Al., 2016; Molaei et al., 2018 **2)** ACS Omega 2022, 7, 22406−22420: Consiglieri et al., 2010; Javaheri et al., 2014 **3)** Mhaske & Sahasrabudhe, 2011; staub et.al. 2010 **4)** Connors & Elder, 2004; Van der Meer et al., 1980 **5)** Ministry of health, 2014 **6)** Fatmawati et.al. 2017 **7)** Winarti et.al 2017

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Review Article

Pharmacological and Physiological Effects on different organ systems of post covid-19 individuals, a review

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ABSTRACT

The coronavirus illness 2019 (COVID-19) pandemic, caused by the novel virus SARS-CoV-2, has brushed the globe, hitting nearly every country. The death toll from COVID-19 continues to climb because it is extremely contagious and has no definitive cure at this time. The lungs are the primary organ to be harmed with diffuse alveolar involvement because SARS-CoV-2 is conveyed mostly via droplets. Failure of other organ systems has also been recorded, resulting in myositis, disseminated intravascular coagulation, and acute renal injury. Furthermore, cytokine storm has been proposed as a potentially fatal consequence of COVID-19. We hope to amalgamate current understanding about the impact of SARS-CoV-2 on multiple organ systems and prognosis in this study which will assist in early detection and taking preventive and curable measures against COVID-19.

Keywords: Covid-19, organs and systems, coronary syndrome, anosmia, ace2 receptors, etc.

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INTRODUCTION

The COVID-19 epidemic, which began in Wuhan, China, has now spread worldwide, infecting millions of people. It was seen to be highly homologous to the SARS coronavirus (SARS-CoV), which was responsible for the respiratory pandemic during the 2002–2004 period. **[1,2]** This virus refers to a group of related viruses belonging to family Coronaviridae and subfamily Orthocoronavirinae. Its name is derived from the Latin word "corona", meaning crown, based on the electron microscopic appearance of small spiky bulbar projections called peplomers. As an RNA virus, coronavirus is also a positive single-stranded enveloped virus known to be infective for birds and mammals. Seven coronaviruses are identified to cause disease in humans and most of these viruses belong to one of the following two groups, i.e. alpha coronaviruses (229E and NL63) and beta coronaviruses (OC43 and HKU1) [1]. Experience told us the coronaviruses may cause mild to moderate symptoms in common. As of April 7th, 2020, around 1,400,000 cases worldwide have been reported according to the Centre for Systems Science and Engineering (CSSE) at John Hopkins University**.[3]** COVID-19 has a wide range of effects on practically all organs and systems, as detailed in this article.

Acute coronary syndrome, congestive heart failure, myocarditis, and arrhythmias are among the conditions that can be caused by it in the heart. Kidney damage is frequently the result of underlying systemic issues. Even young individuals can have a stroke. Seizures and delirium are common side effects. There are reports of anosmia and a loss of taste. Patients and providers alike suffer from psychological issues. The stool could be infected with this virus. Lactate dehydrogenase levels may be high. Various skin symptoms have been recorded, including a patchy erythematous rash. The most common symptoms reported after SARS-CoV-2 infection include fever, dry cough, and fatigue, with less common reports of loss of appetite, sputum production, rhinorrhea, sneezing, sore throat, myalgia, diarrhea, conjunctivitis, headache, loss of taste or smell, skin rash, and discoloration of fingers or toes. The most serious symptoms present as dyspnea, shortness of breath, and chest pain or pressure**.[4]**

The virus binds to ACE2 receptors in vascular endothelial cells, the heart, the brain, the kidneys, the colon, the liver, the pharynx, and other tissues. It has the potential to harm these organs directly. In addition, the virus's systemic problems cause organ malfunction. This is a summary of COVID-19's wide-ranging effects on almost all organs and systems. Inflammation, endotheliitis, vasoconstriction, hypercoagulability, and edema are all symptoms of this condition. There is lymphocytopenia, increased D-dimer, elevated fibrin degradation products (FDPs), and disseminated intravascular coagulation (DIC). There are reports of deep vein thrombosis (DVT), venous thromboembolism (VT), pulmonary embolism (PE), systemic and pulmonary arterial thrombosis and embolism, ischemic stroke, and myocardial infarction (MI). With the common symptoms arthralgia, myalgia, chest tightness, sore throat, anorexia and diarrhea are some of the lesser common symptoms. However, the classical triad of fever, cough, and dyspnoea are seen in 15% of the patients [4]. COVID-19 is similar to seasonal flu in terms of symptoms, spread pattern, as it transmits mainly through droplets and its predilection for

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lung tissues. However, with a worldwide prevalence of about 9343 infections per million population and the mortality as high as 2.3%, COVID-19 has posed a major health concern to humanity [5]. Compared to seasonal flu, COVID-19 has a longer incubation period and is more contagious [6]. Though the symptoms may appear by the 5th day, the incubation period varies from 2 to 15 days. Patients with COVID-19 can be contagious 2 days before the development of the first symptom and continue to be infective up to 10 days. Lack of a definite treatment, unavailability of vaccines, possible mutation of the virus, and an unpredictable progression of the disease further aggravate. These patients possess severe pneumonia or complication such as ARDS, myocarditis, septic shock, venous thromboembolism, and multi-organ failure. Being a novel disease, COVID-19 was first reported in December 2019, and not much is known regarding its pathophysiological basis and progression yet. However, experience from SARS and MERS told us that understanding the pathophysiological basis and progression of the virus' predecessors can help figure out its effect on various systems and components leading to multi-organ failure. Henceforth the current review highlights the pharmacological and physiological effects and happening in different organs and systems of COVID-19 attacked individuals.

Pulmonary effects:

The lung infection from the Covid-19 starts from the lower respiratory tract when the angiotensin-converting enzyme 2 located in the alveolar cells is invaded and damaged by the virus.**[5]** According to autopsy findings, the individuals had characteristic diffuse alveolar destruction without organization and fibrosis in the acute period. Disruption of endothelium and alveolar cells causes it. This causes fluid and cellular exudation, as well as the creation of a hyaline membrane. There are additional cases of acute fibrinous and organizing pneumonia. Alveolar fibrin aggregation is the cause. Inflammation of the airways is evident. Alveolar and interstitial edemas are caused by increased capillary permeability. COVID-19 has vascular angiogenesis as a differentiating trait. Patients with COVID-19 have subpleural and peripheral regions of ground-glass opacity and consolidation on chest CT scans. The majority of the patients have distribution on both sides. Patchy infiltrates can be seen on chest radiographs, and they may be spread asymmetrically. Immediately after recovery from the Covid-19 patients are most likely to suffer from shortness of breath or dyspnea as well as fatigue**. [6]** The solidified aggregates of lesions blocked the blood vessels around and within the alveoli due to the disease. **[7]** Respiratory insufficiency can be treated in a variety of ways. These patients receive oxygen through a high-flow nasal cannula, as well as noninvasive breathing. Positioning yourself prone may help you get more oxygen.

Cardiac effects:

Cardiovascular issues can occur before or after pulmonary and other symptoms in COVID-19. Patients with established coronary artery disease (CAD), latent CAD, and without CAD can all suffer from ischemic heart damage. Plaque rupture and thrombosis are the principal causes of the first two. The last one is caused by a lack of oxygen and looks like a heart attack. Antiplatelet and anticoagulation medication may be effective for acute coronary

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syndrome caused by plaque rupture. Percutaneous coronary intervention and fibrinolytic treatment may be explored. During the COVID-19 period, however, the reported incidence of acute MI has decreased. In a German study of 100 patients who recently recovered from COVID-19, cardiac magnetic resonance imaging (performed a median of 71 days after COVID-19 diagnosis) revealed cardiac involvement in 78% and ongoing myocardial inflammation in 60%. **[8]** The virus has been seen invading myocytes in some patients. Without direct viral penetration, a systemic inflammatory response such as cytokine storm can cause myocarditis.Acute cardiac damage and heart failure affects about half of the non-survivors. The early stages of the disease are dominated by respiratory failure, while the latter stages are dominated by cardiac injury. SARS-CoV-2 also triggers hypercytokinaemia which could provoke myocardial damage due to systemic inflammation. **[9, 10]** Diabetes, obesity, age, and hypertension, all of which are vascular risk factors, have a stronger link to death than respiratory disease. In the United Kingdom, diabetics accounted for one-quarter of COVID-19 deaths, while chronic pulmonary disease patients accounted for 15%.

There is heart failure and an increase in brain-type natriuretic peptide (BNP). Troponin and BNP levels beyond a certain threshold are linked to death. Troponin and BNP levels can both rise as a result of PE. Heart failure may be induced by a worsening demand-supply relationship in elderly people with CAD or hypertension. In younger individuals, myocarditis is more likely to be the reason. Long after the virus has been cleared and the patient has recovered, cardiovascular problems can emerge. Inflammation might go unnoticed for a long time. Many survivors of severe acute respiratory syndrome (SARS), which is strongly connected to COVID-19, developed dyslipidemia, pulmonary fibrosis, and avascular necrosis over time. Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers are commonly used drugs that have not been shown to enhance the risk of COVID-19 infection or associated consequences and should not be stopped drugs, or a combination of the two.

Renal effects:

COVID-19 makes it more difficult to manage dialysis and kidney transplant patients. The specific mechanism of kidney involvement is unknown; however, it is likely multifactorial. **[11, 12**] Chronic renal disease was present in roughly 15% of the patients who died in the United Kingdom. The kidneys contain ACE2 receptors. The virus can be discovered in the kidneys' glomerular cells, tubular epithelium, and podocytes. Acute kidney injury (AKI) is frequently caused by systemic disorders such as diabetes, hypertension, chronic renal disease, hypoxia, and coagulopathy. AKI and severe hypoperfusion can result from cytokine storms. Early and close follow-up in acute kidney injury may assist COVID-19 survivors with persistently reduced renal function. **[13]**

Rhabdomyolysis, which can be triggered by hyperventilation or drugs like remdesivir, can potentially cause acute renal injury. In New York, over 90% of mechanically ventilated patients suffered AKI. AKI happens at the same time as respiratory failure. Peritoneal dialysis is being used more frequently due to a paucity of continuous renal replacement treatment and other hemodialysis equipment and supplies.

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In hospitalized patients, especially those who are unstable, the latter is unsatisfactory. Peritoneal dialysis catheters are commonly inserted in the front abdomen. It has a lower effectiveness in people who are prone due to respiratory failure. The difficulty is solved by placing the catheter on the side of the abdomen. Fever is prevalent in around half of kidney transplant recipients at first, and diarrhea is present in roughly a quarter of the patients. They have a faster illness progression and a greater mortality rate than a matched cohort.

Effect on brain:

The cerebral cortex and brain stem both have ACE2 receptors. Meningitis and encephalitis are symptoms of viral infection of the central nervous system in some persons (CNS). The brain stem reflexes, particularly the one that detects oxygen deprivation, are depressed. Neurological symptoms may be the sole ones present, or they may appear alongside respiratory or other symptoms. Although stroke is a serious albeit uncommon consequence of acute COVID-19, encephalitis, seizures, and other conditions such as major mood swings and "brain fog" have been reported up to 2 to 3 months after initial illness onset**.[14]** People with more severe disease are more likely to have neurological signs. They could be caused by changes in oxygen and carbon dioxide levels. Dizziness, headaches, and altered awareness, such as disorientation, delirium, and inability to rouse, are some of the symptoms. Delirium is a frequent condition that can cause long-term cognitive impairment, including memory problems. Benzodiazepines are being used for sedation due to a lack of regularly used sedatives such propofol and dexmedetomidine. A cytokine storm can produce inflammation and edema in the brain. Sympathetic storm can elicit seizure-like symptoms in some patients. Even in young people with no prior history of stroke, a blockage of a brain artery can cause a stroke. This is due to hypercoagulability and endothelial damage, in part. There is also a risk of cerebral bleeding. There may be ataxia and seizures. It's possible that the cranial nerves are implicated. Anosmia and dysgeusia, or a loss of taste, have been recorded. Symptoms include nerve pain, skeletal muscle weakness and pain, as well as tingling or numbness in the hands and feet. Rhabdomyolysis might result in an increase in serum creatine kinase. Encephalopathy, agitation, and confusion were common neurological symptoms among ARDS patients in the ICU. Enhanced tendon reflexes, ankle clonus, and bilateral extensor plantar reflexes are corticospinal tract symptoms. The coronavirus infection culminated in a high prevalence of prolonged neurological impact termed as Post COVID-19 Neurological Syndrome (PCNS). **[15]**

Gastrointestinal effect:

Patients with COVID-19 experience diarrhea, nausea, vomiting, loss of appetite, and abdominal pain or discomfort, and these symptoms might start before or occur with or without other symptoms such as fever, myalgia, and cough. **[16]** These symptoms may appear before or after other symptoms such as fever, myalgias, or cough, and they may occur with or without accompanying symptoms. ACE2 receptors are abundant in the lower GI tract. Some patients' faeces includes whole infectious viruses, whereas others just have RNA and protein fragments. It takes longer for those with a virus in their stool to eliminate it. Despite the fact that only a tiny fraction of patients experience GI symptoms, up to half of those who do shed

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virus in their stool. The virus protein shell can also be discovered in the cells of the stomach, duodenum, and rectal mucosa. Lactate dehydrogenase and other liver enzymes are high in more than half of COVID-19 hospitalized patients, indicating liver or bile duct impairment. This is most likely the case.

Emotional Health and Well-being

In addition to symptom persistence and clinical squeal that may last far beyond the initial COVID-19 illness, the extent of emotional and behavioural concerns and general distress for those affected has yet to be determined. A diagnosis ofCOVID-19, and subsequent need for physical distancing, has been associated with feelings of isolation and loneliness**.[17]**

COVID-19–related stigma has also become pervasive and can result in a sense of hopelessness. Increasing reports of lingering malaise and exhaustion akin to chronic fatigue syndrome may leave patients with physical debility and emotional disturbance. Compounded by the psychological toll of the pandemic experienced population wide, individuals recovering from COVID-19 may be at even greater risk of depression, anxiety, posttraumatic stress disorder, and substance use disorder. These combined effects have the potential to result in a global health crisis, considering the sheer number of COVID-19 cases worldwide.

Effect on skin:

Only 3% of patients noted a skin rash at 6 months follow-up in the post-acute COVID-19 Chinese study**.[18]** COVID-19 has skin signs that are similar to other viruses and chronic inflammatory illnesses such as acne, eczema, psoriasis, and rosacea. Neurogenic, microthrombotic, or immune complex-mediated vascular disorders can cause cutaneous symptoms. The majority of patients with cutaneous symptoms exhibit a patchy erythematous rash. Some people get urticaria or hives all over their bodies. A few people experience fluid-filled vesicles or blisters that look like chickenpox. They can get rashes that look like measles. The trunk is the most usually affected location. Itching is either minimal or non-existent. Some people get skin eruptions when their symptoms first appear, while others develop them after they've been admitted to the hospital. In most cases, lesions heal within a few days. The severity of COVID-19 is unrelated to skin symptoms. Patients may acquire livedo reticularis as a result of their treatment. It's a purplish net-like darkening of the skin that's usually caused by blood clotting issues. On the arms, legs, and buttocks, there are lacy, dark rashes with dead skin cells. They're linked to a condition called hypercoagulability. Petechiae can be found. There may be a nonpruritic blanching livedoid vascular eruption, possibly due to vaso-occlusion. They appear as mottled red or pink patches with a net-like appearance. Chilblains, which are purple, slightly hard, and often tender, are also present. Frostbite-like spots on COVID toes and fingers with a red or purple rash or hive-like eruption. Ongoing investigations may provide insight into potential immune or inflammatory mechanisms of disease.**[19]**

Effect on coagulation:

There isn't a lot of bleeding in COVID-19. Deep vein thrombosis (DVT), venous thromboembolism (VT), pulmonary embolism (PE) and cor pulmonale (cor pulmonale), systemic and pulmonary arterial thrombosis and embolism, ischemic stroke, and myocardial infarction have all been

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reported (MI). DVT and PE are common among the dead. This is caused by inflammation, platelet activation, hypercoagulability, endothelial dysfunction, blood vessel constriction, stasis, hypoxia, muscle immobility, and disseminated intravascular coagulation (DIC). Fever and inflammation produce hypercoagulability and poor fibrinolysis. Mechanisms of thromboinflammation include endothelial injury, complement activation, platelet activation and platelet–leukocyte interactions, neutrophil extracellular traps, release of pro-inflammatory cytokines, disruption of normal coagulant.**[20]** The cytokine interleukin-6 (IL-6) is associated to hypercoagulability and the severity of disease. Increased antiphospholipid antibodies have been linked to thrombosis. The liver produces more procoagulant substances than other organs. The time to activated partial thromboplastin and the time to prothrombin are both measured in minutes.C-reactive protein levels are elevated. DIC, lymphocytopenia, elevated D-dimer, high fibrin degradation products (FDPs), and cytokine storm are all connected to significant systemic inflammation. The levels of D-dimer and DIC are prognostic.

Guidelines suggest that thromboprophylaxis be used. Prophylaxis with low-molecular-weight or regular heparin, fondaparinux, or a direct oral anticoagulant like apixaban or rivaroxaban, or a direct oral anticoagulant like apixaban or rivaroxaban, or a direct oral anticoagulant like apixaban or rivaroxaban, should be considered. COVID-19 spike proteins bind to heparins tightly, preventing the virus from infecting cells. Heparins also inhibit the generation of IL-6 and the activation of the immune system. In patients who require assisted respiration, systemic anticoagulation may cut mortality without causing substantial bleeding, according to a nonrandomized experiment. In ARDS caused by other factors, however, systemic anticoagulation has not been found to be useful.

Inflammation and endothelititis:

When compared to other health disorders, COVID-19 can cause white blood cells to produce far more cytokines. The cytokine storm, also known as hypercytokinemia or cytokine release syndrome, maybe preceded by and contribute to a surge of catecholamines. Systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), multi-organ damage, shock, and mortality can all result from this maladaptive response. Even if the virus load is decreasing, the inflammatory response may continue to rise. SARS-CoV-2 infects endothelial cells in a variety of organs, resulting in widespread lymphocytic endothelins and vasoconstriction. Hypoperfusion occurs as a result of the inflammation, hypercoagulability, and edema that accompany it, resulting in organ ischemia. COVID-19, on the other hand, does not affect patients with pre-existing immune-mediated inflammatory illness who are being treated with anti-cytokine biologics and other immunomodulatory medications. SARS-CoV-2 infects the host using the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed in several organs, including the lung, heart, kidney, and intestine. ACE2 receptors are also expressed by endothelial cells.**[21]**

Effect on eyes:

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Conjunctivitis is the most common ophthalmic manifestation documented in COVID-19 patients. In a large series of cases with mild COVID-19 infection, Sindhuja *et al*. reported that 11/127 (8.66%) patients had conjunctivitis.**[22]** Both ACE2 receptors and TMPRSS2 proteases are located in ocular surface cells in the cornea, inside the eyelids, and in the white of the eye, which are required for SARS-CoV-2 infection. Ocular disorders, such as conjunctivitis, affect about one-third of hospitalized patients. Conjunctivitis is more common in patients who are ill. Early ocular involvement is possible. Ocular surface cells serve as virus entrance points and reservoirs. The shedding of the ocular virus is a cause of infection. The virus can remain infectious in the eye for up to three weeks.

CONCLUSION:

The SARS-CoV-2 virus attaches to ACE2 receptors found throughout the body, causing harm to practically every system. It can result in a cytokine storm leading to death. Different organs in different people may be damaged, with a temporal course independent of viral load. Complications are caused by inflammation, platelet activation, hypercoagulability, endothelial dysfunction, blood vessel constriction, stasis, hypoxia, hypoperfusion, and muscle immobility. Lungs are frequently impacted including diffuse alveolar destruction withoutorganization and fibrosis. There could be Acute Coronary Syndrome, cardiac failure, or myocarditis present. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers should be continued by patients. AKI is frequently caused by systemic problems. There are cases of meningitis, encephalitis, encephalopathy, stroke, and delirium. The senses of smell and taste are impaired. Viruses enter the body through the eyes, which can potentially be a cause of infection with early ocular involvement. Patients and providers alike suffer from psychological issues. There are signs of gastrointestinal distress including formation of virus protein shells in the cells of the stomach, duodenum, and rectal mucosa. Lactate dehydrogenase and other liver enzymes are high in more than half of COVID-19 hospitalized patients, indicating liver or bile duct impairment. A third of patients with dysexecutive syndrome experience inattention, disorientation, or poorly coordinated movements in response to command after they leave the ICU. The most common skin symptom is a patchy erythematous rash. As a result, COVID-19 can impact almost any organ in the body.

Conflict of Interest

The authors declare ‘no conflict of interest.’

Acknowledgments

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References

1. Yuki K, Fujii M, Koutsogiannaki S. COVID-19 pathophysiology: a review [published online ahead of print, 2020 Apr 20]. Clin Immunol. 2020; 215:108427.

2. Ksiazek TG, Erdman D, Goldsmith CS, et al. Group A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med 2003;348:1953–66.

3. JHUoMCr center, Journal (2020), https://coronavirus.jhu.edu/map.html.

4. Chen, G., Wu, D., Guo, W., Cao, Y., Huang, D., Wang, H., et al. 2020. Clinical and immunological features of severe and moderate coronavirus disease 2019.J. Clin. Invest. 130(5): 2620–2629. doi:10.1172/JCI137244. PMID:32217835.

5. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, & Zuo W. (2020a). Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-Nov. biorxiv The Preprint Server For Biology

6. Carfì, A., Bernabei, R., & Landi, F. (2020). Persistent symptoms in patients after acute COVID-19. Jama, 324(6), 603-605.

7. Wang, Y., Dong, C., Hu, Y., Li, C., Ren, Q., Zhang, X., & Zhou, M. (2020). Temporal changes of CT findings in 90 patients with COVID-19 pneumonia: a longitudinal study. Radiology, 296(2), E55-E64.

8. Puntmann VO, Carerj ML, Wieters I, et al.Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. Published online July 27, 2020. doi:10.1001/jamacardio.2020.3557

9. Ye, Q., Wang, B., & Mao, J. (2020). The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. Journal of infection, 80(6), 607-613.

10. Inciardi, R. M., Lupi, L., Zaccone, G., Italia, L., Raffo, M., Tomasoni, D., ... & Metra, M. (2020). Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). JAMA cardiology, 5(7), 819-824.

11. Askari, H., Sanadgol, N., Azarnezhad, A., Tajbakhsh, A., Rafiei, H., Safarpour, A. R., & Omidifar, N. (2021). Kidney diseases and COVID-19 infection: causes and effect, supportive therapeutics and nutritional perspectives. Heliyon, 7(1), e06008.

12. Benedetti, C., Waldman, M., Zaza, G., Riella, L. V., & Cravedi, P. (2020). COVID-19 and the kidneys: an update. Frontiers in medicine, 7, 423.

13. Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M. V., McGroder, C., Stevens, J. S., & Wan, E. Y. (2021). Post-acute COVID-19 syndrome. Nature medicine, 27(4):601-615.

14. Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review.*JAMA Neurol*. 2020;77(8):1018-1027. doi:10.1001/jamaneurol.2020.2065

15. Wijeratne, T., & Crewther, S. (2020). Post-COVID 19 Neurological Syndrome (PCNS); is a novel syndrome with challenges for the global neurology community. Journal of the Neurological Sciences, 419.

16. Jain, U. (2020). Effect of COVID-19 on the Organs. Cureus, 12(8). e9540.

17. Galea S, Merchant RM, Lurie N. The mental health consequences of COVID-19 and physical distancing: the need for prevention and early intervention. *JAMA Intern Med*. 2020;180(6):817-818. doi:10.1001/jamainternmed.2020.1562

ISSN: 2790-7120

18. Huang, C. et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* **397**, 220–232 (2021).

19. Genovese, G., Moltrasio, C., Berti, E. & Marzano, A. V.Skin manifestations associated with COVID-19: current knowledge and future perspectives.*Dermatology* **237**, 1–12 (2020).

20. Ramlall, V. et al. Immune complement and coagulation dysfunction in adverse outcomes of SARS-CoV-2 infection. *Nat. Med.* **26**, 1609–1615 (2020).

21. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 2005; 111: 2605–10.

22. Sindhuja K, Lomi N, Asif MI, Tandon R. Clinical profile and prevalence of conjunctivitis in mild COVID-19 patients in a tertiary care COVID-19 hospital: A retrospective cross-sectonal study Indian J Ophthalmol. 2020;68:1546–5

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Research Article

Application of machine learning classifiers for predicting non-institutional delivery in Bangladesh: Evidence from the Bangladesh Demographic and Health Survey, 2017-18

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ABSTRACT

The primary goal of this study was to investigate the performance of various machine learning classifiers for non-institutional delivery prediction in the Bangladeshi context. The target sample for this study was 5338 live births in the three years before the survey which was collected from a nationally representative survey dataset. After the association test, significant explanatory variables were used in six popular supervised algorithms, such as logistic regression, random forest, support vector machine, k-nearest neighbor, naïve bayes, and elastic net regression. The performance of these six classifiers was evaluated by some model evaluating parameters, like, Accuracy, sensitivity, specificity, Cohen's kappa statistic, and AUC value. Approximately 51% of live births occur in Bangladesh without any institutional care. The bivariate analysis result showed that first birth age, parental education, wealth status, religion, mass media, women's working status, child ever born, region, and residence had a significant influence on non-institutional delivery in Bangladesh. According to the six classifiers results, this study found the logistics regression algorithm (accuracy = 67.3, AUC = 73.5%) provides the most accurate classification for predicting non-institutional birth in Bangladesh. The main strength of this study was that it compared different machine learning algorithms by well-known model evaluation parameters to predict non-institutional deliveries. Therefore, plans and guidelines should be developed to improve the significant factors that are related to childbirth.

Keywords: Machine learning, institutional birth, non-institutional birth, maternal mortality

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INTRODUCTION

Maternal mortality due to inadequate health services during childbirth is one of the major public health challenges in low- and middle-income countries (Xu et al., 2022). According to global estimates, more than 3 million women died from pregnancy-related complications (Ekholuenetale et al., 2020), and the highest percentage of deaths were found from sub-Saharan Africa, and south Asian region (Musarandega et al., 2021; Ahmed et al., 2018). A recent study using nationally representative survey data estimates that more than two-thirds of women of childbearing age in the African region died in childbirth (Ekholuenetale et al., 2020). South Asian countries still face enormous public health challenges, particularly in relation to maternal and newborn health (Akhter and Alam, 2019). So, it is important to ensure health facilities during delivery for childbearing mothers.

Place of delivery is considered as the most fundamental stage of the utilization of maternal health care services. A recent study in Nepal found that about half of marginalized women gave birth to their last child in a non-institutional setting (Devkota et al., 2020). Another study in Bangladesh, using three consecutive Bangladesh Multiple Indicator Cluster Surveys, showed an increasing trend in the provision of health services in Bangladesh (Kabir et al., 2022). Though it was increased, the actual proportion is not satisfactory. Talukder et al., (2022) conducted a comparative study base on Bangladesh Demographic and Health Survey dataset and estimate that more than 60% of women in Bangladesh do not used institutional facilities during their childbirth. This rate was higher than India (18.9%) (Patel et al., 2021) and Pakistan (27.7%) (Sadia et al., 2022).

Obviously child bearing is an important life event for a women and health care during child birth is the best marker of maternal wellbeing. The cause behind for non-institutional delivery are complex and heterogenous. According to several literatures, maternal age at first birth, education (Barman et al., 2020), religion (Huda et al., 2019), wealth status (Ganle et al., 2019), mass media (Huda et al., 2019), residential area (Yaya et al., 2017) and so on were significantly influenced the choice of the place of delivery. But proper diagnosis and intervention on delivery service can lessen the risk of maternal mortality, and the actual target of diagnosis procedure is to predict risk cases accurately. As a risk prediction model, machine learning classifiers are widely used in public health sector (Hossain et al., 2022). To best our knowledge, there were no previous literature that used machine learning classifiers on maternal delivery facilities sector. Based on this literature gap, this study set its objective. The major objective was to evaluate

prediction performance of various well-known machine learning classifiers by using model evaluation parameters.

2. Materials and Methods

2.1. Data source

The analysis of this study based on Bangladesh Demographic and Health Survey, 2017-18 which is a nationally representative survey data and financially supported by the United States Agency for International Development (USAID) in Bangladesh.

2.2. Sampling design and sample size

A two-stage stratified sampling procedure used by the authority of Bangladesh Demographic and health survey (BDHS), where 675 enumeration areas (EAs) were selected in the first stage. The survey used the list of the enumerated area (EA) of the population and housing census of Bangladesh in 2011 provided by the Bangladesh Statistics Office (BBS). In second stage, 30 households were selected from each EA. In the survey, 20250 household were selected and 20217 reproductive aged women were interviewed. The actual target sample for this study was number of live births by 15-49 aged women in the last years from the survey. So, based on this criterion, the weighted and final sample size was 5338.

2.3. Dependent variable

The Bangladesh Demographic and Health Survey, 2017-18 collect information of live births by place of delivery. This study categorized this information into two categories as, “Non-institutional birth” and “Institutional birth”. Non-institutional birth included birth at respondent’s home, delivery hut, and other place except any medical institution. On the other side, the institutional birth includes birth at medical college hospital (both public and private), specialized government hospital, district hospital, MCWC, upazila health complex, public sector, UH & family welfare center, medical clinic (community, private, NGO).

2.4. Independent variables

A set of categorical explanatory variables were selected. According to various studies, fourteen explanatory variables were considered as independent variables, namely Region (Northern, Southern, Central, Eastern), Residence (Urban, Rural), Age at first birth (<20, ≥20), Wealth status (Poor, Middle, Rich), Women’s educational level (No education, Primary education, Secondary and above), Husband’s educational level (No education, Primary education, Secondary and above), Respondent’s working status (Yes, No), Religion (Islam, Others), Mass media access (Yes, No), Children ever born (1, 2-3, 4+).

2.5. Statistical analysis

A simple descriptive analysis was used in this study to get percentage distribution of the study participants. In bi-variate setup, this study examines the association between the outcome variable and the explanatory variables. In this case, the chi-square test of independence was used which formula can be written as,

$$\chi^2 = \sum \frac{(O_i - E_i)^2}{E_i}$$

O_i and E_i be the observed and expected frequency, respectively. The χ^2 statistic asymptotically follows the χ^2 distribution with $(r-1)(c-1)$ degrees of freedom, where r be the number of categories in independent variable and c be the number of categories in dependent variable.

The main outcome variable of this study had binary response. Let, Y_i be the binary dependent variable where,

$$Y_i = \begin{cases} 1; Birth\ occurs\ at\ non-instutional\ place \\ 0; Birth\ occurs\ at\ institutional\ place \end{cases}$$

Because of this binary nature, this study applied six well known machine learning classifiers which was widely used in public health sector. These are,

1. Logistic regression (LR) (Hajmeer and Basheer, 2003)
2. Random Forest (RF) (Pal, 2005)
3. Support Vector Machine (SVM) (Golpour et al., 2020)
4. K Nearest Neighbors (KNN) (Güvenç et al., 2021)
5. Naïve Bayes (NB) (Golpour et al., 2020)
6. Elastic Net Regression (ENR) (Richmond et al., 2020)

2.6. Propose approach

Before fitting these supervised models, data cleaning and preparation is mandatory. For instances, it is important to exclude all missing values from the data set. Then randomly divide the data into two parts: Training data set, which was used to train the data, and testing data set, which was used to evaluate the training performance of the data set. In this case, this study used 70% of total data as training data, and rest 30% of the data as testing data. To overcome the overfitting or underfitting problem of training, this study applied 10-fold repeated cross-validation on the training data set, and then evaluate the performance by using various evaluation parameter from testing data set. The following seven model evaluation parameters were used,

i. $Accuracy = \frac{TP+TN}{TP+TN+FP+FN}$

ii. $Recall/Sensitivity = \frac{TP}{TP+FN}$

iii. $Specificity = \frac{TN}{TN+FP}$

iv. $Precision/\ Positive\ predictive\ value = \frac{TP}{TP+FP}$

v. $Negative\ predictive\ value = \frac{TN}{TN+FN}$

vi. $Cohen's\ Kappa\ (\kappa)$ statistic used to assess the performance of a classification model which range between 0 and 1. If the

value of κ<0, then we may conclude that there was no agreement. Similarly, $0 < \kappa < 0.20$ indicates slightly agreement, $0.21 < \kappa < 0.40$ indicates fairly agreement, $0.41 < \kappa < 0.60$ indicates moderately agreement, $0.61 < \kappa < 0.80$ indicates substantial agreement, and $\kappa > 0.81$ indicates almost perfect agreement (McHugh, 2019).

vii. *Area under the ROC curve* (AUC) is a best performance measurement than accuracy for classification problems where higher the value of AUC indicates the better model (Ling, Huang and Zhang, 2003).

2.7. Analytical tools

For data management and analysis, the SPSS (Statistical Package for Social Science) 25 version and R-programming version 4.0.0 were used.

3. Results

Table 1 shows the percentage distribution of live births in the three years preceding the survey according to the selected sociodemographic characteristics. Slightly less than one-quarter of live births occur in urban areas, while over three-quarters are in rural Bangladesh. Among the total sample, the majority of live births were from Muslim households (92%), and from the central region of Bangladesh. It was found that 70.5% of live births were recorded for those mothers who gave birth to their first child when they were under 20 years old. A higher percentage of the parents of living children (65.9% for women and 51.5% for husbands) had completed secondary and higher education levels. With regard to household wealth status, a larger portion of live births were from poor households (approximately 42%). The proportion of people who accessed any type of media (TV, radio, or newspaper) was approximately 55%. From Table 1, it can be said that two-thirds of the total women who gave live births in the three years preceding the survey had no employment status (except household work), and approximately half of the women (approximately 50%) gave birth to 2-3 live births during their reproductive age period.

The prevalence of non-institutional delivery and the background characteristics of the selected covariates are also shown in Table 1. This finding indicates that approximately 51% of live births in Bangladesh take place in non-institutional settings. From the χ^2 the test, all the covariates were found to be significant association with non-institutional delivery in Bangladesh (P<0.001). The prevalence of non-institutional delivery by a reproductive aged women was found to be higher for the eastern region of Bangladesh (approximately 56%), rural Bangladesh (55.4%), women with an early birth age (57%), women with poor wealth status (68%), women and their partners without education (74% and 69%, respectively), employed women (59%), women who were

not accessed by mass media (64.2%), women with a 4+ CEB (72.8%), and Muslim religious women (51.6%)

Table 1. Percentage distribution and association between selected covariates and non-institutional delivery in Bangladesh.

Variables	Frequency (%)	Non-institutional delivery in Bangladesh		
		Yes (%)	No (%)	χ^2value (p-value)
Age at first birth (in years)				
<20	3765 (70.5)	57.0	43.0	208.09 (<0.001)
≥20	1573 (29.5)	35.3	64.7	-
Women's education				
None	351 (6.6)	74.1	25.9	403.828 (<0.001)
Primary	1471 (27.6)	68.6	31.4	-
Secondary+	3515 (65.9)	40.8	59.2	-
Husband's education				
None	802 (15.0)	69.6	30.4	397.77 (<0.001)
Primary	1789 (33.5)	62.2	37.8	-
Secondary+	2747 (51.5)	37.6	62.4	-
Wealth status				
Poor	2214 (41.5)	68.1	31.9	568.26 (<0.001)
Middle	1020 (19.1)	51.6	48.4	-
Rich	2104 (39.4)	31.8	68.2	-
Religion				
Islam	4910 (92.0)	51.6	48.4	23.07 (<0.001)
Others	428 (8.0)	39.5	60.5	-
Mass media access				
No	2417 (45.3)	64.2	35.8	324.54 (<0.001)
Yes	2921 (54.7)	39.4	60.6	-
Working status				
Yes	1973 (37.0)	59.0	41.0	88.20 (<0.001)
No	3365 (63.0)	45.7	54.3	-
CEB				

1	1931 (36.2)	39.2	60.8	244.61 (<0.001)
2-3	2711 (50.8)	53.0	47.0	-
4+	696 (13.0)	72.8	27.2	-
Region				
Southern	785 (14.7)	47.6	52.4	28.28 (<0.001)
Central	1809 (33.9)	47.7	52.3	-
Eastern	1567 (29.4)	56.1	43.9	-
Northern	1177 (22.1)	49.8	50.2	-
Residence				
Rural	3911 (73.3)	55.4	44.6	135.24 (<0.001)
Urban	1427 (26.7)	37.4	62.6	-
Non-institutional delivery				
Yes	2702 (50.6)			-
No	2636 (49.4)			-

In this study, six different machine learning algorithms were used to classify non-institutional delivery as yes or no in the test data set. The prediction performance of these algorithms is compared using performance parameters such as accuracy, sensitivity, and specificity. In addition, Cohen's k statistic was used to determine the discrimination accuracy of the algorithm. The prediction results of non-institutional delivery with performance parameters for each machine learning algorithm (for training and testing data sets) are shown in Table 2.

Using a logistic regression classifier, the accuracy in the test data set was 67.30%, the sensitivity was 70.78%, and the specificity was 63.20%. The model tuning parameter for the linear support vector machine is the cost parameter, which is denoted by C. The value of C may be found by a cross-validation procedure. This study found the value of the cost parameter is 0.1, and then the support vector machine (linear) showed 63.84% accuracy, with 71.13% sensitivity, and 55.27% specificity in predicting the non-institutional delivery of the experimental observation results.

The accuracy, sensitivity, and specificity of the random forest algorithm were reported as 67.17%, 75.79%, and 57.05%, respectively. In this case, two types of model improvement parameters were applied from a cross-validation approach, such as, the number of variables randomly sampled and the number of trees to growth.

However, the performance shown by the k-nearest neighbor algorithm was 66.60%, 72.18%, and 60.05%, accuracy, sensitivity, and specificity, respectively. Naive Bayes showed an accuracy of 66.67%, a sensitivity of 72.64%, and a specificity of 60.47% in predicting the non-institutional delivery of the test observation results.

This study also applied the elastic net regression model, which was a combination of two penalty functions (α) which produced an improvement over lasso and ridge regression. After 10-fold cross-validation, this study got the model parameter α=0.43 and the model accuracy was 67.04% with a sensitivity of 72.64% and a specificity of 60.47%.

According to the accuracy value of test data, the best result was achieved by the logistic regression algorithm, which showed that accuracy was 67.30%, indicating that the algorithm is 67.30% correct for the prediction. The Cohen kappa statistics of all classifiers recommended adopting a "fairly agreement".

Table 2. Performance indicators of all the six machine learning algorithms for predicting pregnancy intention among married women in Bangladesh.

	LR	**RF**	**SVM**	**KNN**	**NB**	**ENR**
Training data set						
Accuracy (%)	68.85	69.44	65.27	68.85	68.44	68.74
95% CI	(67.33, 70.34	(67.93, 70.92	(63.71, 66.80)	(67.33, 69.88)	(66.92, 69.94)	(67.22, 70.23)
κ	0.3698	0.3772	0.2932	0.3694	0.3663	0.3663
Sensitivity (%)	73.98	78.71	74.03	74.38	69.44	75.07
Specificity (%)	62.82	58.55	54.98	62.35	67.27	61.30
PPV (%)	70.03	69.04	65.88	69.88	71.36	69.50
NPV (%)	67.27	70.08	64.32	67.45	65.21	67.68
Test data						
Accuracy (%)	67.30	67.17	63.84	66.60	66.67	67.04
95% CI	(64.93, 69.60)	(64.80, 69.48	(61.42, 66.20)	(64.23, 68.92)	(64.29, 68.98)	(64.67, 69.35)
κ	0.3404	0.3319	0.2661	0.3241	0.3316	0.3329
Sensitivity (%)	70.78	75.79	71.13	72.18	66.94	72.64
Specificity (%)	63.20	57.05	55.27	60.05	66.35	60.47
PPV (%)	69.33	67.46	65.14	67.98	70.04	68.35

NPV (%)	64.80	66.72	61.96	64.75	63.07	65.29
PPV = Positive Predictive Value, NPV = Negative Predictive value						

Although accuracy is a parameter for evaluating performance, there were some drawbacks with this parameter. In order to calculate accuracy, the value of accuracy may vary by changing the cutoff point value. In this case, the area under the ROC curve is an alternative to comparing the machine learning classifiers. Depending on the AUC value in Figure 1, this study concludes that the logistic regression classifier produces the highest AUC value (approximately 73%) among all classifiers. That is, this model was 73% correct for prediction purposes.

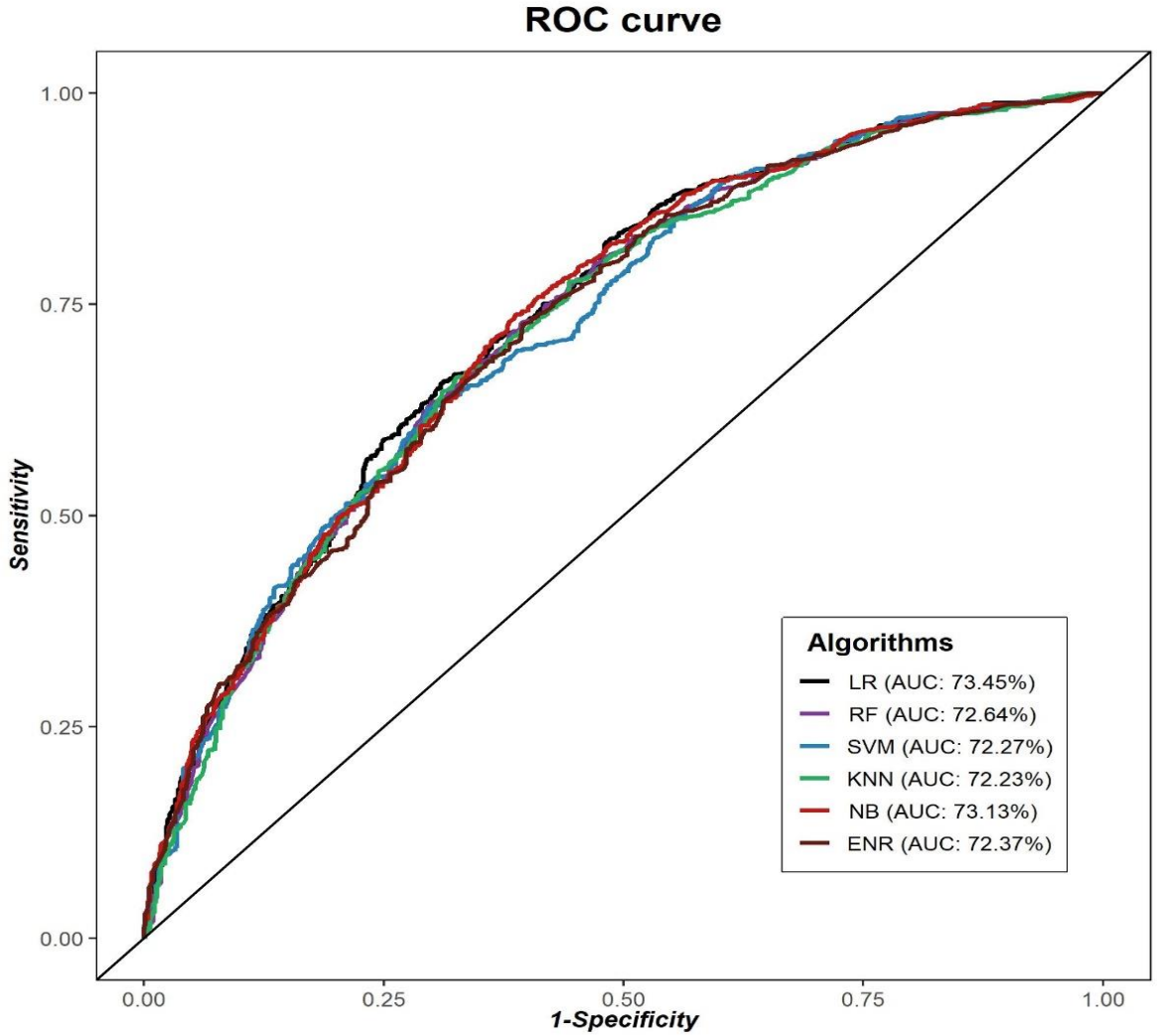

Figure 1. Performance evaluation of classification techniques using area under the ROC curve.

4. Discussion

The main objective of this study was to explore an approximately better model for in-sample prediction of non-institutional delivery in Bangladesh. To achieve this objective, we used six popular machine learning classifiers and compared their prediction performance using the area under the ROC curve (AUC) value. Many authors have made comparisons based on accuracy measurement (Talukder and Ahammed, 2020; Nayan et al., 2022), which have a drawback. The accuracy measurement value may differ depending on the cut point. In this situation, area under the ROC curve is used as an alternative (Ling et al., 2003).

We trained all models on the training data set using 10-fold repeated cross validation and extracted evaluation parameter values from the test data set. This study applied the χ^2 test to test the association between the dependent and independent variables.

This study found that about half of the live births occur at a non-institutional place in Bangladesh, which was 10% better than the estimate using the 2014 Bangladesh Demographic and Health Survey data (Talukder et al., 2022). According to a prevalence analysis, the prevalence of non-institutional delivery was higher for mothers who had their first child before the age of 20. Uneducated parents always choose a non-institutional setting for childbirth. These findings were consistent with previous studies (Nigusie et al., 2020; Limenih and Deyesa, 2016).

Access to media can improve the knowledge of healthcare facilities among women and their husbands. This study noted that maximum non-institutional birth occurs for women who have less connection to mass media (reading newspapers or magazines, listening to the radio, and watching television), which follows the results of the previous studies (Mills et al., 2007).

Women from poor families had a higher prevalence of delivering a child in a non-institutional setting than individuals from affluent households. A previous study conducted by Neupane et al., (2021) revealed similar findings using a multivariate model.

Place of residence is an important factor in the choice of delivery place in Bangladesh. Rural women had a higher prevalence of giving birth in non-institutional places than urban women. Previous research has also found that women in urban areas have a better childbirth experience than women in rural areas (Abeje et al., 2014; Gebremichael and Fenta, 2021).

We discovered that the logistic regression (LR) classifier had the highest AUC value among the machine learning classifiers (approximately 73%). Along this line, we can presume that the LR algorithm predicts non-institutional delivery in Bangladesh as moderately superior to any other machine learning algorithm. The LR algorithm also

has the best prediction power when predicting the risk of low birth weight in Bangladesh (Pollob et al., 2022). Another study conducted by Khare et al., (2017) So based on our study and prior literature, we recommend applying the popular logistic regression classifier when the prediction of non-institutional delivery is the core interest of Bangladesh.

5. Strengths and Limitations

This study applied six well-known machine learning algorithms to examine the prediction performance of non-institutional delivery in Bangladesh. The cross-validation provided a reliable estimate of the model evaluation parameters. Despite these strengths, this study had some limitations, such as the fact that, because it used a secondary data set, it couldn't utilize many important factors that are major contributors to non-institutional delivery in Bangladesh, and the cross-sectional data couldn't establish causal links.

6. Conclusions

We compiled six ML algorithms in this study to predict whether a mother will give birth in a non-institutional setting given some risk factors. Among the algorithms considered, the LR algorithm performed better than others based on AUC. Additionally, our findings would be valuable for identifying the associated factors of non-institutional delivery in Bangladesh. Therefore, plans and guidelines should be developed to improve significant factors that are related to non-institutional delivery in Bangladesh.

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Competing interest

The authors declare that they have no conflicts of interest.

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This research did not receive any fund.

Author's contributions

Conceived and designed the experiments, MIH; Performed the experiments; Analyzed and interpreted the data, MIH and FAZ. Original draft preparation, MIH and FAZ. Review and editing, MIH, FAZ, AR, and MIHN. All authors have read and agreed to the final version of the manuscript.

Data availability statements

The Bangladesh Demographic and Health Survey is publicly available at https://dhsprogram.com/data/available-datasets.cfm.

References

Abeje, G., Azage, M. and Setegn, T. (2014). Factors Associated with Institutional Delivery Service Utilization among Mothers in Bahir Dar City administration, Amhara region: a Community Based Cross Sectional Study. *Reproductive Health*, 11(22). doi:10.1186/1742-4755-11-22.

Ahmed, I., Ali, S.M., Amenga-Etego, S., Ariff, S., Bahl, R., Baqui, A.H., Begum, N., Bhandari, N., Bhatia, K., Bhutta, Z.A., Biemba, G., Deb, S., Dhingra, U., Dube, B., Dutta, A., Edmond, K., Esamai, F., Fawzi, W., Ghosh, A.K. and Gisore, P. (2018). Population-based rates, timing, and Causes of Maternal deaths, stillbirths, and Neonatal Deaths in South Asia and sub-Saharan Africa: a multi-country Prospective Cohort Study. *The Lancet Global Health*, 6(12), pp.e1297–e1308. doi:10.1016/s2214-109x(18)30385-1.

Akhter, H. and Alam, Md.M.R. (2019). Understanding the Trends of Maternal and Neonatal Mortality in Bangladesh in the Context of South Asia. *Advances in Anthropology*, 9(1), pp.56–69. doi:10.4236/aa.2019.91004.

Barman, B., Roy, A., Zaveri, A., Saha, J. and Chouhan, P. (2020). Determining Factors of Institutional Delivery in India: a Study from National Family Health Survey-4 (2015–16). *Clinical Epidemiology and Global Health*, 8(4), pp.1335–1340. doi:10.1016/j.cegh.2020.05.007.

Devkota, B., Maskey, J., Pandey, A.R., Karki, D., Godwin, P., Gartoulla, P., Mehata, S. and Aryal, K.K. (2020). Determinants of Home Delivery in Nepal – a Disaggregated Analysis of Marginalised and non-marginalised Women from the 2016 Nepal Demographic and Health Survey. *PLOS ONE*, 15(1), p.e0228440. doi:10.1371/journal.pone.0228440.

Ekholuenetale, M., Benebo, F.O. and Idebolo, A.F. (2020). Individual-, household-, and community-level Factors Associated with Eight or More Antenatal Care Contacts in Nigeria: Evidence from Demographic and Health Survey. *PLOS ONE*, 15(9), p.e0239855. doi:10.1371/journal.pone.0239855.

Ganle, J.K., Mahama, M.S., Maya, E., Manu, A., Torpey, K. and Adanu, R. (2019). Understanding Factors Influencing Home Delivery in the Context of User-fee Abolition in Northern Ghana: Evidence from 2014 DHS. *The International Journal of Health Planning and Management*, 34(2), pp.727–743. doi:10.1002/hpm.2731.

Gebremichael, S.G. and Fenta, S.M. (2021). Determinants of Institutional Delivery in Sub-

Saharan Africa: Findings from Demographic and Health Survey (2013–2017) from Nine Countries. *Tropical Medicine and Health*, 49(45). doi:10.1186/s41182-021-00335-x.

Golpour, P., Ghayour-Mobarhan, M., Saki, A., Esmaily, H., Taghipour, A., Tajfard, M., Ghazizadeh, H., Moohebati, M. and Ferns, G.A. (2020). Comparison of Support Vector Machine, Naïve Bayes and Logistic Regression for Assessing the Necessity for Coronary Angiography. *International Journal of Environmental Research and Public Health*, 17(18), p.6449. doi:10.3390/ijerph17186449.

Güvenç, E., CetinG.Ç. and Koçak, H. (2021). Comparison of KNN and DNN Classifiers Performance in Predicting Mobile Phone Price Ranges. *Advances in Artificial Intelligence Research*, 1(1), pp.19–28.

Hajmeer, M. and Basheer, I. (2003). Comparison of Logistic Regression and Neural network-based Classifiers for Bacterial Growth. *Food Microbiology*, 20(1), pp.43–55. doi:10.1016/s0740-0020(02)00104-1.

Hossain, Md.I., Habib, Md.J., Saleheen, A.A.S., Kamruzzaman, Md., Rahman, A., Roy, S., Amit Hasan, Md., Haq, I., Methun, Md.I.H., Nayan, Md.I.H. and Rukonozzaman Rukon, Md. (2022). Performance Evaluation of Machine Learning Algorithm for Classification of Unintended Pregnancy among Married Women in Bangladesh. *Journal of Healthcare Engineering*, 2022, pp.1–10. doi:10.1155/2022/1460908.

Huda, T.M., Chowdhury, M., El Arifeen, S. and Dibley, M.J. (2019). Individual and Community Level Factors Associated with Health Facility delivery: a Cross Sectional Multilevel Analysis in Bangladesh. *PLOS ONE*, 14(2), p.e0211113. doi:10.1371/journal.pone.0211113.

Kabir, S., Hasan, M.R., Hossain, M.I., Suraiya, S., Islam, F.B., Nayan, M.I.H., Haq, I. and Hossain, M.S. (2022). Determinants and Trends of Health Facility Delivery in Bangladesh: a Hierarchical Modeling Approach. *BioMed Research International*, 2022, p.e1359572. doi:10.1155/2022/1359572.

Khare, S., Kavyashree, S., Gupta, D. and Jyotishi, A. (2017). Investigation of Nutritional Status of Children Based on Machine Learning Techniques Using Indian Demographic and Health Survey Data. *Procedia Computer Science*, 115, pp.338–349. doi:10.1016/j.procs.2017.09.087.

Limenih, A. and Deyesa, N. (2016). Assessing the Magnitude of Institutional Delivery Service

Utilization and Associated Factors among Mothers in Debre Berhan, Ethiopia. *Journal of Pregnancy and Child Health*, 3(3). doi:10.4172/2376-127x.1000254.

Ling, C.X., Huang, J. and Zhang, H. (2003). AUC: A better measure than accuracy in comparing learning algorithms. In: Y. Xiang and B. Chaib-draa, eds., *Advances in Artificial Intelligence. Canadian AI 2003. Lecture Notes in Computer Science*. Berlin Heidelberg: Springer, pp.329–341.

McHugh, M.L. (2019). Interrater reliability: the Kappa Statistic. *Biochemia medica*, 22(3), pp.276–82.

Mills, S., Williams, J.E., Adjuik, M. and Hodgson, A. (2007). Use of Health Professionals for Delivery following the Availability of Free Obstetric Care in Northern Ghana. *Maternal and Child Health Journal*, 12(4), pp.509–518. doi:10.1007/s10995-007-0288-y.

Musarandega, R., Nyakura, M., Machekano, R., Pattinson, R. and Munjanja, S.P. (2021). Causes of Maternal Mortality in Sub-Saharan Africa: a Systematic Review of Studies Published from 2015 to 2020. *Journal of Global Health*, 11. doi:10.7189/jogh.11.04048.

Nayan, M.H., Uddin, Ms.G., Hossain, M., Alam, M., Zinnia, M., Rahman, M., Ria, R. and Haq Methun, M. (2022). Comparison of the Performance of Machine learning-based Algorithms for Predicting Depression and Anxiety among University Students in Bangladesh: a Result of the First Wave of the COVID-19 Pandemic. *Asian Journal of Social Health and Behavior*, 5(2), p.75. doi:10.4103/shb.shb_38_22.

Neupane, B., Rijal, S., GC, S. and Basnet, T.B. (2021). A Multilevel Analysis to Determine the Factors Associated with Institutional Delivery in Nepal: Further Analysis of Nepal Demographic and Health Survey 2016. *Health Services Insights*, 14, p.117863292110248. doi:10.1177/11786329211024810.

Nigusie, A., Azale, T. and Yitayal, M. (2020). Institutional Delivery Service Utilization and Associated Factors in Ethiopia: a Systematic Review and META-analysis. *BMC Pregnancy and Childbirth*, 20(364). doi:10.1186/s12884-020-03032-5.

Pal, M. (2005). Random Forest Classifier for Remote Sensing Classification. *International Journal of Remote Sensing*, 26(1), pp.217–222. doi:10.1080/01431160412331269698.

Patel, R., Marbaniang, S.P., Srivastava, S., Kumar, P. and Chauhan, S. (2021). Why Women Choose to Deliver at Home in India: a Study of prevalence, factors, and socio-economic

Inequality. *BMC Public Health,* 21(1785). doi:10.1186/s12889-021-11779-5.

Pollob, S.M.A.I., Abedin, Md.M., Islam, Md.T., Islam, Md.M. and Maniruzzaman, Md. (2022). Predicting Risks of Low Birth Weight in Bangladesh with Machine Learning. *PLOS ONE*, 17(5), p.e0267190. doi:10.1371/journal.pone.0267190.

Richmond, H.L., Tome, J., Rochani, H., Fung, I.C.-H., Shah, G.H. and Schwind, J.S. (2020). The Use of Penalized Regression Analysis to Identify County-Level Demographic and Socioeconomic Variables Predictive of Increased COVID-19 Cumulative Case Rates in the State of Georgia. *International Journal of Environmental Research and Public Health*, 17(21), p.8036. doi:10.3390/ijerph17218036.

Sadia, A., Mahmood, S., Naqvi, F., Naqvi, S., Soomro, Z. and Saleem, S. (2022). Factors Associated with Home Delivery in Rural Sindh, Pakistan: Results from the Global Network Birth Registry. *BMC Pregnancy and Childbirth*, 22(192). doi:10.1186/s12884-022-04516-2.

Talukder, A. and Ahammed, B. (2020). Machine Learning Algorithms for Predicting Malnutrition among Under-Five Children in Bangladesh. *Nutrition*, 78, p.110861. doi:10.1016/j.nut.2020.110861.

Talukder, A., Anik, B., Hossain, M., Haq, I. and Habib, M. (2022). Socioeconomic and Demographic Factors for mothers' Delivery at home: a Comparative Study among BDHS 2007, 2011 and 2014. *Asian Journal of Social Health and Behavior*, 5(1), p.10. doi:10.4103/shb.shb_160_21.

Xu, Y., Peng, M.Y.-P., Ahuru, R.R., Anser, M.K., Osabohien, R. and Aziz, A. (2022). Individual and community-level Factors Associated with non-institutional Delivery of Women of childbearing-age in Nigeria. *Humanities and Social Sciences Communications*, 9(1). doi:10.1057/s41599-022-01168-7.

Yaya, S., Bishwajit, G. and Ekholuenetale, M. (2017). Factors Associated with the Utilization of Institutional Delivery Services in Bangladesh. *PLOS ONE*, 12(2), p.e0171573. doi:10.1371/journal.pone.0171573.

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Review Article

Health Hazards of Mercury and arsenic as heavy metals

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ABSTRACT

Mercury and arsenic have severe hazardous effects to human health. These two heavy metals have been extensively studied and their effects on human health regularly reviewed by international bodies such as the WHO. These metals have been used by humans for thousands of years. Although several adverse health effects of Hg and As have been known for a long time, exposure continues, and is even increasing in some parts of the world, in particular in less developed and some developing countries. The general population is primarily exposed to mercury via food, fish being a major source of methyl mercury exposure, and dental amalgam. The general population does not face a significant health risk from methyl mercury, although certain groups with high fish consumption may attain blood levels associated with a low risk of neurological damage. Since mercury exposure is a risk to the fetus, in particular, pregnant women should avoid a high intake of certain fish, having mercury content. Exposure to arsenic is mainly via intake of food and drinking water which are the most important sources. Chronic exposure to

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arsenic in drinking-water is mainly related to increased risks of skin cancer and lesions. Occupational exposure to arsenic, primarily by inhalation, is causally associated with lung cancer.

Keywords: Health hazards, Heavy metals, Exposure, Contamination, Occasional poisoning etc.

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INTRODUCTION

Heavy metals are commonly defined as those having a specific density of more than 5 g/cm.[1] Mercury and arsenic are two important heavy metals, have severe hazardous effects to human health. These hazards are associated with exposure to mercury (Organic mercury, Inorganic mercury and gaseous mercury) and arsenic as metalloid. [2] These two metals have been used in many different areas of the world for thousands of years. Mercury was allegedly used by the Romans as a balm to alleviate teething pain in infants, and was later (from the 1300s to the late 1800s) employed as a remedy for syphilis. Although adverse health effects of heavy metals have been known for a long time, exposure to heavy metals continues and is even increasing in some areas. Mercury is still used in gold mining in many parts of Latin America and Arsenic is still common in wood preservatives. Since the middle of the 19th century, production of heavy metals increased steeply for more than 100 years, with concomitant emissions to the environment.[3] Emissions of heavy metals to the environment occur via a wide range of processes and pathways, including to the air e.g. from combustion, extraction and processing. In this way they come to the surface waters (via runoff and releases from storage and transport) and to the soil and into ground waters and crops. Atmospheric emissions tend to be of greatest concern in terms of human health, both because of the quantities involved and the widespread dispersion and potential for exposure that often ensues. The spatial distributions of mercury emissions to the atmosphere in Europe and other countries can be found in the Meteorological Synthesizing Centre. Distribution of anthropogenic mercury emissions reflects mainly the level of coal consumption in different regions. People may be exposed to potentially harmful chemical, physical and biological agents of air, food, water or soil.[4] However, exposure does not result only from the presence of a harmful agent in the environment. The prime way of happening is from contaction. There must be contact between the agent and the outer

surface of the human body, such as the airways, the skin, eyes or the mouth. Exposure is often defined as a function of concentration and time: "an event that occurs when there is contact at a boundary between a human and the environment with a contaminant of a specific concentration for an interval of time".[1]

Mercury

Occurrence:

The mercury compound cinnabar (HgS), was used in pre-historic cave paintings for red colours, and metallic mercury was used as a cosmetic to lighten the skin. In medicine, mercury is used as a treatment for syphilis and as diuretics [calomel (Hg_2Cl_2)], and mercury amalgam is still used for filling teeth in many countries.[5] Metallic mercury is used in thermometers, barometers and instruments for measuring blood pressure. A major use of mercury is in the chlor- alkali industry, in the electrochemical process of manufacturing chlorine, where mercury is used as an electrode.

Exposure and dose: The largest occupational group exposed to mercury is dental care staff. During the 1970s, air concentrations in some dental surgeries reached 20 µg/m1, but since then levels have generally fallen to about one-tenth of those concentrations. Inorganic mercury is converted to methyl mercury, which is very stable and accumulates in the food chain. Until the 1970s, methyl mercury was commonly used for control of fungi on seed grain. The general population is primarily exposed to mercury via food, [6] and dental amal- gam.[7] Mercury in urine is primarily related to (relatively recent) exposure to inorganic compounds, and blood mercury may be used to identify exposure to methyl mercury. Peoples have exposure from surface of human autopsy, as well as from samples of blood, urine and plasma.[8]

Health effects:

Inorganic mercury

Mercury exposure may give rise to lung damage, tremor, changes in personality, restlessness, anxiety, sleep disturbance and depression. The symptoms are reversible after cessation of exposure. Because of the blood–brain barrier there is no central nervous involvement related to inorganic mercury exposure. Metallic mercury may cause kidney damage, which is reversible by exposure stoppage. It is revealed the occurrence of proteinuria at relatively low levels of occupational exposure. Metallic mercury may cause contact eczema, and mercury from amalgam fillings may give rise to oral lichen. It has been feared that mercury in amalgam may cause a variety of symptoms called 'amalgam disease' is, however, controversial, and although some authors claim proof of symptom relief after removal of dental amalgam fillings[9].

Organic mercury

Methyl mercury poisoning has a latency of 1 month or longer after acute exposure, and the main symptoms relate to nervous system damage [10] eg parestesias and numbness in the hands and feet, coordination difficulties and concentric constriction, auditory symptoms. High doses may lead to death, usually 2–4 weeks after onset of symptoms. The Minamata catas- trophe in Japan in the 1950s was caused by methyl mercury poisoning from fish contaminated by mercury discharges to the surrounding sea. In the early 1970s, more than 10,000 persons in Iraq were poisoned by eating bread baked from mercury-polluted grain, and several thousand people died as a consequence of the poisoning. However, the general population does not face significant health risks from methyl mercury exposure with the exception of certain groups with high fish consumption. A high dietary intake of mercury from consumption of fish has been hypothesized to increase the risk of coronary heart disease,[11] myocardial infarction.[1] Mercury levels were significantly correlated with fish consumption, and the mean mercury level was higher in dentists than in non-dentists.

Arsenic

Occurrence:

Arsenic is a metalloid, occurred in rock, soil, water and air. Inorganic arsenic is present in groundwater used for drinking in several countries all over the world including Bangladesh, Chile and China, whereas organic arsenic compounds eg, arsenobetaine etc. are primarily found in fish, which thus may give rise to human exposure.[12] Smelting of non-ferrous metals and the production of energy from fossil fuel are the two major industrial processes that lead to arsenic contamination of air, water and soil.[13] Other sources of contamination are the manufacture and use of arsenical pesticides and wood preservatives. Concentrations in air in rural areas range from µg /1 to 4 ng/m3, concentrations in cities may be as high as 200 ng/m3and it may much higher (1000 ng/m3) in near industrial sources. Water concentrations are usually □10 □g/l, although higher concentrations may occur near anthropogenic sources. Levels in soils usually range from 1 to 40 mg/kg, but pesticide application and waste disposal can result in much higher concentrations.[14] General population exposure to arsenic is mainly via intake important source food and drinking water. Contaminated soils such as mine-tailings are also a potential source of arsenic exposure.[14]

Exposure and dose: Absorption of arsenic in inhaled airborne particles is highly

dependent on the solubility and the size of particles. Fat soluble arsenic compounds are easily absorbed from the gastrointestinal tract. However, water soluble arsenic is extensively methylated in humans and the metabolites are excreted in the urine.[14] Arsenic concentrations in blood, hair, nails and urine have been used as biomarkers of exposure which are useful indicators of past arsenic exposure. Speciated metabolites in urine expressed as either inorganic arsenic or the sum of metabolites (inorganic arsenic + MMA + DMA) is generally the best estimate of recent arsenic dose. However, consumption of certain seafood may confound estimation of inorganic arsenic exposure. [14]

Health effects

Inorganic arsenic is acutely toxic and intake of large quantities leads to gastrointestinal, cardiovascular and central nervous systems and peripheral vascular severity, and eventually death. In survivors, bone marrow depression, haemolysis, hepatomegaly, melanosis, polyneuropathy and encephalopathy may be observed. Populations exposed to arsenic via drinking water show excess risk of mortality from lung, bladder and kidney cancer, skin cancer and lesions. Studies on various populations exposed to arsenic by inhalation, such as smelter workers, pesticide manufacturers and miners in many different countries consistently demonstrate an excess lung cancer. The latest WHO evaluation[14] concludes that arsenic exposure via drinking water is causally related to cancer in the lungs, kidney, bladder and skin. Uncertainties in the estimation of past exposures are important when assessing the exposure–response relationships, but it would seem that drinking water arsenic concentrations of approximately 100 µg/l have led to cancer at these sites, and that precursors of skin cancer have been associated with levels of 50–100 µg /l. There is relatively strong evidence for hypertension and cardiovascular disease in diabetes and reproductive effects, cerebrovascular disease, long-term neuro- logical effects, and cancer at other sites.[1]

Conclusions

Recent data indicate that the hazardous health effects of acute and chronic mercury and arsenic heavy metal exposure and poisoning may cause various adverse health effects which are become very severe, complex and life threatening, and even sometime be the reason of death. The general population does not face a significant health risk from methylmercury, although certain groups with high mercury containing fish consumption may attain blood levels

associated with a low risk of neurological damage to adults. Since there is a risk to the fetus in particular, pregnant women should avoid a high intake of certain fish, such as shark, swordfish, tuna, pike, walleye and bass, etc. Long-term exposure to arsenic in drinking water is mainly related to increased risks of skin cancer, but also some other cancers, and other skin lesions including hyperkeratosis and pigmentation changes. Occupational exposure to arsenic, primarily by inhalation, is causally associated with lung cancer. But some health hazards of these heavy metals poisoning is still controversial and unresolved which required more and further study to prevent the associated contamination, problems and severity.

References

1. NRC. Human Exposure Assessment for Airborne Pollutants. Advances and Opportunities. Washington, DC: National Research Council, National Academy Press, 1991

2. Järup L. Hazards of heavy metal contamination. British medical bulletin. 2003 Dec 1;68(1):167-82.

3. Fashola MO, Ngole-Jeme VM, Babalola OO. Heavy Metal Pollution from Gold Mines: Environmental Effects and Bacterial Strategies for Resistance. Int J Environ Res Public Health. 2016 Oct 26;13(11):1047. doi: 10.3390/ijerph13111047. PMID: 27792205; PMCID: PMC5129257.

4 Jarup L, Berglund M, Elinder CG, Nordberg G, Vahter M. Health effects of cadmium exposure— a review of the literature and a risk estimate. Scand J Work Environ Health 1998; 24 (Suppl 1): 1–51

5 WHO. Inorganic Mercury. Environmental Health Criteria, vol. 118. Geneva: World Health Organization, 1991

6. WHO. Methyl Mercury. Environmental Health Criteria, vol. 101. Geneva: World Health Organization, 1990

7. Sallsten G, Thoren J, Barregard L, Schutz A, Skarping G. Long-term use of nicotine chewing gum and mercury exposure from dental amalgam fillings. J Dent Res 1996; 75: 594–8

8. Salonen JT, Seppanen K, Nyyssonen K, Korpela H, Kauhanen J, Kantola M, Tuomilehto J, Esterbauer H, Tatzber F, Salonen R. Intake of mercury from fish, lipid peroxidation, and the risk of myocardial infarction and coronary, cardiovascular, and any death in eastern Finnish men. Circulation 1995; 91: 645–55

9. Guallar E, Sanz-Gallardo MI, van't Veer P, Bode P, Aro A, Gomez-Aracena J, Kark JD, Riemersma RA, Martin-Moreno JM, Kok FJ; Heavy Metals and Myocardial Infarction Study Group. Mercury, fish oils, and the risk of myocardial infarction. N Engl J Med 2002; 347: 1747–54

10 WHO. Arsenic and Arsenic Compounds. Environmental Health Criteria, vol. 224. Geneva: World Health Organization, 2001

11 Chilvers DC, Peterson PJ. Global cycling of arsenic. In: Hutchinson TC, Meema KM (eds) Lead, Mercury, Cadmium and Arsenic in the Environment. Chichester: John Wiley & Sons, 1987; 279–303

12. Buchet JP, Lauwerys R, Roels H, Bernard A, Bruaux P, Claeys F, Ducoffre G, DePlaen P, Staessen J, Amery A, Lijnen P, Thijs L, Rondia D, Sartor F, Saint Remy A, Nick L. Renal effects of cadmium body burden of the general population. *Lancet* 1990; **336**: 699–702
13. Jarup L, Hellstrom L, Alfven T, Carlsson MD, Grubb A, Persson B *et al.* Low level exposure to cadmium and early kidney damage: the OSCAR study. *Occup Environ Med* 2000; **57**: 668–72
14. Barbee Jr JY, Prince TS. Acute respiratory distress syndrome in a welder exposed to metal fumes. *South Med J* 1999; **92**: 510–2