Naturally Found Alkaloids from Plants Showing Antiviral Activities

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (B. Pharm)

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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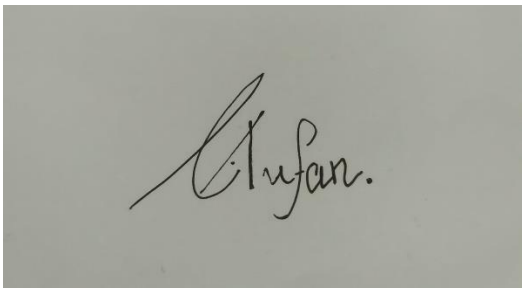

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APPROVAL

The thesis/project titled "Naturally Found Alkaloids from Plants Showing Antiviral Activities" submitted by Nilufar Akhter Disha (18146067) of Spring, 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on March 2023.

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Ethics Statement

This study does not involve any kind of animal trial or human trial.

Abstract

Herbal medicine it is used to promote health, prevent illness, and treat illness, including viral infections like HIV, HSV, and many others. A less expensive kind of medicine, herbal medicine is distinct from modern medicine in content, practice, as well as philosophy. Nitrogenous chemical substances found in plants called alkaloids can affect human physiology, with three types: true alkaloids, proto alkaloids, and pseudo alkaloids. There are several naturally occurring alkaloids with antiviral properties against a wide range of diseases. Worldwide, herbal medications are being created, but it is challenging to obtain standardization, stability, and quality control.

Keywords: herbal drug, herbal medicine, alkaloids, advantages, disadvantages, antiviral activity, plant source, alkaloid, plant parts, treatments, pathogen etc.

Dedication

Dedicated to all my teachers and my parents.

Acknowledgement

First of all, all the praises to the Almighty. I am thankful to Almighty for giving me the health, knowledge and chance to accomplish this project.

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Chapter 1

Introduction

According to recommendations issued by the World Health Organization (WHO) in 1996, herbal drugs is made up of active final products comprising underground or aerial plant parts or plant components, or a mix of both (Jahromi et al., 2021). Traditional herbal medicine is an affordable medical practice that varies in material, technique, and theory from modern medicine and is essential to the health maintenance of the global population. Traditional herbal medicine has its roots in Asia, where it has the longest history of any region in the world (Ru et al., 2014). Herbal medicine is a form of medication that uses the roots, stems, leaves, blossoms, or seeds of plants to promote health, prevent disease, and cure sickness. Herbal medicine originated in ancient cultures. It involves the utilization of healing plants to treat disease and enhance peoples' health and wellness. Some plants have substantial elements and should be utilised with the same degree of caution as prescription drugs. A specialist CAM treatment, such as herbal medicine, may be classified as conventional medicine with the aid of supporting scientific data and clinical research. Given the present positive cultural perspective on herbal remedies, their appeal across all age groups is growing (Jahromi et al., 2021). Formulas for herbal medicines frequently contain a large number of botanicals, with as many as fifty different species and thousands of chemical components. The absorption, distribution, metabolism, and excretion (ADME) qualities of a medication (Ru et al., 2014).

In general, the evidence supporting the usefulness of herbal medications is scant. Despite the fact that some individuals find them beneficial, their usage is often based on traditional practices rather than scientific study. Herbal remedies are typically used to improve health and treat chronic ailments rather than those that are life-threatening. Traditional treatments are increasingly used when conventional medicine fails to treat illness, as is the case with advanced

cancer and new infectious diseases. Herbal remedies are commonly regarded as safe and effective. Pharmaceutical medications are precise in their activities and pathology targeting, but herbal remedies may have a wide variety of physiological effects. There are "drug-like" herbal cures whose effects are comparable to those of pharmaceuticals. During the last three decades, the usage of herbal medicines and supplements has skyrocketed, with more than 80 percent of the global population depending on them in some capacity for basic healthcare. The biological activity of alkaloids, which are naturally occurring phytochemicals, is well known. Many of these compounds have been intensively researched for their broad-spectrum antiviral actions against various DNA and RNA viruses (Abookleesh et al., 2022).

Medicinal herbs utilized in traditional Persian medicine have also shown significant benefits for the treatment of NDs (Moradi et al., 2020). Globally, around 80% of consumers utilize herbal medicine (HMs) or other natural products. Depending on their socioeconomic class, ethnicity, and cultural practices, the rate might range from 7% to 55% among pregnant women (Illamola et al., 2019).

Herbal remedies originated in ancient societies. It includes the therapeutic use of plants to cure illness and improve overall health. Some plants contain strong chemicals and should be used with the same degree of care as prescription drugs. Herbal use may prevent and treat cardiovascular disease, cancer, and diabetes. Moreover, it may prevent blood clots and has anti-inflammatory and anticancer activities. Ongoing research indicates that garlic, linseed, fenugreek, and lemongrass may help reduce cholesterol. One of the most diverse classes of secondary metabolites found in living things are alkaloids, which have a vast range of structural variations, biosynthesis methods, and pharmacological effects. Historically, plants have been used to extract most alkaloids. It is also present in humans, animals, insects, marine invertebrates, and microorganisms. For hundreds of years, many alkaloids have been used in medicine, and some of them are still important today. As alkaloids have been employed as

medications in potions, medicines, teas, poultices, and poisons for four thousand years, alkaloids are as ancient as civilization itself. Chinese herbal medicine has played and continues to play a significant part in the health care of humans in China and other Asian nations. In anti-cancer research, natural compounds derived from Chinese herbal therapy (CHT) have also become a "hot issue." In the last several decades, Chinese herbal medicine has also been acknowledged globally as a valuable source for the development of innovative medications (Luo et al., 2019). The usage of herbal medicines (HMs), including medicinal plants as botanical medications, beverages, nutritional supplements, and indigenous formulations containing herbs, has exploded over the past two decades. (Illamola et al., 2019).

Chapter 2

Objectives of the Study

This paper provides an extensive overview of the antiviral properties of naturally occurring alkaloids. This research intends to examine the efficacy of the promising medication candidates. The information for this review paper came from the following sources such as peer-reviewed research, news articles, academic publications, and websites. In addition, publications from major journals like Springer, Nature, Cells, The Lancet, MDPI, Frontiers, Bio pharma, and Taylor and Francis were examined for this research. Numerous periodicals were perused for data and information that assisted in determining the antiviral activities and mechanisms of the potent drugs. All the information was compiled and referenced properly, resulting in a greater understanding. There have been efforts to uncover data gaps and omissions in the existing literature. Nonetheless, more than 120 clinical trials have been started to discover the powerful medication mechanism. The objective of was to examine and demonstrate the antiviral properties of naturally occurring plant alkaloids. Herbal medicine is seen as a potentially practical and accessible way for the recovery of a large number of ailments in a world now afflicted by a variety of illnesses. The objective of the study was to discover and collect the most promising medication candidates. Alkaloids derived from natural sources have been utilized to treat numerous conditions with astounding success, along within everyday living. Many alkaloids, such as Hypaconitine, Songorine, Mesaconitine, Aconitine, Melicopteline, Berberine, and Anisomycin, shown antiviral properties. Thus, the primary objective of this work was to collect and display all of them in accordance.

Chapter 3

3.1 Methodology

For this project, multiple search engines were used to obtain scholarly publications and books. PubMed, science direct, google scholar, nature, Elsevier, Web of Knowledge, Mendeley, research gate, NCBI resources, and Scopus were utilized as sources of published literature. In order to obtain the information that was necessary for the topic, several surveys were investigated. The years 2010 and 2022 are included in this range of publication dates for the studies. In addition, essential information and terminology was compiled from the aforementioned several areas.

We looked for appropriate articles using the following keywords: herbal medication, herbal medicine, alkaloids, benefits, drawbacks, antiviral activity, plant source, alkaloid, plant components, therapies, pathogen, etc.

3.2 Material and method

This research was carried out via a strategy that included a combination of different methodologies. We took use of Google scholar, PubMed, Web of Science, Science Hub as well as other similar resources.

After the selection of the relevant articles and papers, thorough research was conducted on all of them. Hence, the paper was concluded. Several websites, including Google Scholar, PubMed, and scientific hubs were consulted since they provide a broader selection of publications and expertise on the subject that was being researched. In addition, they displayed the required articles in the appropriate chronological order, beginning with the specified year and progressing all the way up to the most current items.

3.3 The materials and the sampling techniques

All of the papers utilized for this research were published between 2010 and 2023. In addition, the selected papers displayed proper rationale and outcomes.

Chapter 4

4.1 Antiviral Properties Exhibited by Alkaloids

Tobacco mosaic virus (TMV) and cucumber mosaic virus were both susceptible to the antiviral effects of the alkaloids hypaconitine, songorine, mesaconitine, and aconitine (CMV) (Xu et al., 2019). Indole alkaloid Isatibisindosulfonic acid A3 O β Dglucopyranoside, Isatibisindosulfonic B ,Isatindosulfonic acid A 3 O β D glucopyranoside, Isatindosulfonic B, Isatindosulfonic acid C and Isatindosulfonic acid D showed antiviral activities against Coxsackie, influenza A like pathogens. Displaying IC $_{50}$ values Isatibisindosulfonic acid B seemed to have an IC_{50} value: 0.0009μmol/L and 517.38μmol/L. SI value: 17122.2μmol/L and 3.0μmol/L, respectively, when compared to pleconaril and ribavirin, which served as positive controls. Isatibisindosulfonic acid B and Isatindosulfonic acid B were active against Coxsackie virus B3 and influenza. Isatindosulfonic acid B had IC_{50} values of 33.3 μmol/L and SI 43.0μmol/L (the positive controls oseltamivir and ribavirin had IC501 values of 41.63 μmol/L and 1.06 μmol/L (Meng et al., 2017).

Insatindibisindolamides A and B, two indole alkaloid enantiomers with a new bisindolylacetamide skeleton, demonstrated their antiviral property against influenza and Coxsackie. (Y. F. Liu et al., 2015).

Pathogens such as Influenza, Coxsackie in Vero cells, and Influenza A in MDCK cells were eliminated by alkaloids including 5αhydroxyoxysophocarpine, 12βhydroxyoxysophocarpine, 5αhydroxylemannine, sophocarpine, 5αhydroxysophocarpine, 9αhydroxysophocarpine, 12αhydroxysophocarpine, 12βhydroxysophocarpine, oxysophocarpine, matrine, sophoranol, 9αhydroxymatrine, 14βhydroxymatrine, oxymatrine, 5αhydroxyoxymatrine, 14βhydroxyoxymatrine, and sophoramine (Pan et al., 2015)

The following alkaloids, harmine, harmaline, harmalol, and harman, were found to be effective against influenza A, Puerto Rico pathogens. Vasicine and Vasicinone are additional Quinazoline derivatives. (M. T. Moradi et al., 2017).

In general, flavesine G, flavesine H, flavesine I, flavesine J, alopecurine B, 7,11-dehydro-oxymatrine and 10-oxy-5,6-dehydromatrine are effective against the Hepatitis B Virus, also known as HBsAg. Flavesine G, flavesine H, flavesine I, and flavesine J also have this property (Y. B. Zhang et al., 2018).

Sophaline A, Sophaline B, Sophaline C, and Sophaline D are all examples of alkaloids that displayed antiviral properties with hepatitis B (HBV) in HepG2.2.15 cells, with the results of 24.6% and 19.2% for Sophaline A, 51.0% and 35.2% for Sophaline B, 56.4 and 36% for Sophaline C, and 59.6 and 41.8% for Sophaline D respectively. (Y. B. Zhang et al., 2017)

It was observed that certain alkaloids, including oxoglyantrypine (2a, 2b), cladoquinazoline, epicladoquinazoline, and norquinadoline A, exhibited antiviral activity against influenza virus A. (H1N1) (Peng et al., 2013). In MDCK cells, the antiviral properties of the melicoptelines A, B, C, D, and E were demonstrated against the influenza A viruses H1N1 and H9N2. Among them, melicopteline C demonstrated significantly greater activity (EC50,, $2.57 \pm 0.45\mu M$) and higher selectivity than the positive control ribavirin (EC50, $3.92 \pm 0.79\mu M$) (Lee et al., 2021). Antiviral activities were demonstrated by alkaloids such as Harman and homonojirimycin (HNJ), as well as 2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine, against influenza A virus and influenza A/PR/8/34 virus (H1N1) (G. B. Zhang et al., 2013). The antiviral activities of lycorine AA1, hippeastrine AA2, hemanthamine AA3, and 11-hydroxyvittatine AA4 were demonstrated against avian influenza virus (AIV), influenza virus type A, chickens in Guangdong, 178 in 2004, and influenza virus type A (He et al., 2013). Tetrandrine, TET, Fangchinoline,FAN, and Cepharanthine,CEP fought against MRC5 infection with Coronavirus

OC43 (Kim et al., 2019). Dragmacidin F and D were isolated from the leaves, stem, root, and bark of *Halicortex sp*. Antiviral activity against HIV and HSV as measured by EC50 VALUES: Dragmacidin F – 95.8μM (HSV) -0.91μM (HIV) (Cutignano et al., n.d.). Antiviral alkaloids such as protopine, beta allocryptopine, chelidimerine, Fumarophycine acetate, Corpaine, Sibiricine, sibiricine acetate, and dihydrosibiricine were capable of eliminating pathogens such as the DNA (HSV), PI-3 and Candida albicans. Other pathogens that were also eliminated are Escherichia coli, Proteus mirabilis, Candida albicans, Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus subtilis, Acinetobacter baumannii and Klebsiella pneumoniae (Orhan et al., 2007). Anisomycin is antiviral against Dengue virus (DENV), DENV NS5, (DENV -1-2, -3, -4), and Zika virus (Quintana et al., 2020). Berberine demonstrated antiviral activity against Chikungunya virus (CHIKV), HEK 293T with the CC_{50} of HEK- 293T Berberine- 202.6 micro M $EC_{50\ OF}$LR2006 OPY1 – 37.6 , SGP11-44.2 , CNR20235- 50.9 (Varghese et al., 2016).

Alkaloid	Source	Plant part	Extraction method	Pathogen	Key results	Reference
Hypaconitie, Songorine, Mesaconitie And Aconitine	*Aconitum carmichaelii* Debx	root	ethanol root extract	CMV TMV	IC_{50} values: Curative Rate: (TMV) Hypaconitine f 41.7% Mesaconitine 43.4% Aconitine 42.9% Songorine 17.4% (very low) moderate to high antiviral activity against TMV. bioassay values of 55.3 and 56.6% Curative Rate: (CMV) Hypaconitine 82.4 % Mesaconitine 85.6% They showed moderate to high antiviral activity against CMV.	(Xu et al., 2019).
Indole alkaloid 1.Isatibisindosulfonic acidA 3OβD glucopyranoside , 2.Isatibisindosulfonic acid B 3.Isatindosulfonic acid A3OβDglucopyranoside 4.Isatindosulfonic acid B 5.Isatindosulfonic acid C 6.Isatindos	*Isatis indigotica*	Dried Root	Aqueous	Coxsackie virus B3, influenza A, and influenza A/Hanfang/359/95 (H3N2),	IC_{50} values: Isatibisindosulfonic acid A 3OD glucopyranoside - Isatibisindosulfonic acid B - 33.3 mol/L and SI 4 3.0 Isatindosulfonic acid B – 33.3 mol/L and SI 43.0 (the positive controls pleconaril and ribavirin had IC50 values of 0.0009 and 517.38 μmol/L, and SI values of 17122.2 and 3.0, respectively) (the positive controls oseltamivir and ribavirin had IC50 values of 41.63 and 1.06 μmol/L, respectively, and SI	(Meng et al., 2017).

ulfonic acid D					values of 4773.0 and 1098.2 respectively) Isatindosulfonic acid B and Isatibisindosulfonic acid B were respectively effective against Coxsackie virus B3 and influenza virus A/Hanfang/ 359/95 (H3N2).	
Indole alkaloid: insatindibisindolamides A and insatindibisindolamides B	*Isatis indigotica*	root	aqueous extract	the influenza virus A/Hanfang/ 359/95 and the Coxsackie virus B3 308 (CVB3) (H3N2).	IC_{50} Values: Insatindibisindolamides A – IC50 VALUE: 289 33.3 x10^6 mol/L SI value-5.2, Insatindibisindolamides B IC50 value-33.3 x 10^6 mol/L SI value-5.2	(Y. F. Liu et al., 2015)
1.(+)-5αhydroxy oxysophocarpine , 2.(−)-12β-hydroxyoxysophocarpine , 3.(+)-5α-hydroxylemannines 4.(−)-sophocarpine, 5.(−)-5α-hydroxysophocarpine, 6.(−)-9α-hydroxysophocarpine	*Sophora tonkinensis Gepnep*	Root and rhizomes	Aqueous extract	A/Hanfang/ 359/95 (H3N2) influenza virus, Coxsackie virus B3 in Vero cells, and A/Hanfang/ 359/95 influenza virus in MDCK cells.	IC_{50} values: 12β-hydroxyoxysophocarpine - 26.62 μM 9αhydroxysophocarpine - 197.22 μM sophoranol-252.18μM 14β-hydroxymatrine - 184.14μM hydroxysophocarpine - 440 μM 12α-hydroxysophocarpine - 84.70 μM	(Pan et al., 2015)

7. (+)-12α-hydroxysophocarpine 8. (−)-12β-hydroxysophocarpine 9.(+)-oxysophocarpine 10.(+)-matrine, 11.(+)-sophoranol, 12. (+)-9α-hydroxymatrine, 13.(−)-14β-hydroxymatrine, 14.(+)-oxymatrine, 15. (+)-5α-hydroxyoxymatrine, 16.(−)-14β-hydroxyoxymatrine, 17.(+)-sophoramine					(−)-12β-hydroxysophocarpine - 242.46 μM oxysophocarpine- 402.82 μM (+)-sophoramine- 63.07 μM 12βhydroxyoxysophocarpine,9αhydroxysophocarpine,sophoranol,14β-hydroxymatrine- strong antiviral activity against CVB3. Most potent inhibitors - (+)-12α-hydroxysophocarpine ,(−)-12β-hydroxysophocarpine, (+)-sophoramine (against H3N2)	
β-carbolines: 1.harmine, 2.harmaline 3. harmalol 4. harman. Quinazoline derivatives: 5.vasicine , 6.vasicinone.	*Peganum harmala*	Seeds and root	Ethanol extract	Puerto Rico/8/34 (H1N1,PR8) influenza A	CC50 value of total alkaloid on MDCK cells were 133.9μg/ml CI 95%: 121.9-147 **IC50 values of**: total alkaloid influenza virus 5.8μg/ml CI 95%: 3.7-8.9 SI value of 23.1. **CC50 values**: oseltamivir 539.4 μmol.	(M. T. Moradi et al., 2017)

					SI value - 617.8 CI95%: 378.9- 768.5 0.873 CI95%: 0.55-1.37 This extract's total alkaloids were antiviral, with IC50 of 5.8 (CI95%: 3.7-8.9)µg/ml SI value- 23.1.	
1.flavesine G. 2.flavesine H 3.flavesine I 4.flavesine J 5.alopecurine B 6.7,11dehydro-oxymatrine, 7.10-oxy-5,6dehydromatrine, 8.10-oxysophoridine	*Sophora flavescens*	root	aqueous EtOH	Hepatitis B Virus, HBsAg	HBsAg inhibitory effect: flavesine G- 37.2 % (potent) flavesine H- 30.8 % (less potent) flavesine I - 29.8 % (less potent) flavesine J- 44.3% (potent) alopecurine B -46.0% (potent) 7 ,11-dehydro-oxymatrine -25.4 % 10-oxy-5, 6-dehydromatrine - 33.0% (less potent) 10-oxysophoridine - 32.5 % (less potent) flavesine G, flavesine J, alopecurine B, oxysophoridine significantly inhibited HBsAg secretion with percentage of 37.2%, 44.3%, 46.0%, 38.3%, and 40.2%.	(Y. B. Zhang et al., 2018)
Matrine-Based Alkaloids: 1.Sophaline A,	*Sophora alopecuroides*	seeds	ethanol extract	HBV-infected HepG2.2.15 cells	Inhibitory activity: (HBsAg, HBeAg) Sophaline A 24.6% and 19.2% Sophaline B 51.0% and 35.2 %	(Y. B. Zhang et al., 2017)

2.Sophaline B, 3.Sophaline C, 4.Sophaline D					Sophaline C 56.4 and 36% Sophaline D 59.6 and 41.8%	
1. 3-hydroxyglyantrypine, 2.oxoglyantrypine (2a, 2b), 3.cladoquinazoline, 4.epi-cladoquinazoline, 5.norquinadoline A, 6.quinadoline A, 7.deoxynortryptoquivaline, 8.deoxytryptoquivaline, 9.tryptoquivaline 10.CS-C 11.quinadoline B 12.prelapatin B 13.glyantrypine	derived fungus *Cladosporium sp. PJX-41*.	Mangrove-derived fungus	EtOAc extract	H1N1,influenza virus A.	IC_{50} Values (μM) oxoglyantrypine2b-85μM norquinadolineA-82μM deoxynortryptoquivaline-87μM deoxytryptoquivaline-85μM tryptoquivaline-89μM quinadoline B-82μM (all of them – strong potency) Compound oxoglyantrypine 2b, norquinadoline A, deoxynortryptoquivaline, tryptoquivaline, and quinadoline B showed considerable activity with IC50 values of 85, 82, 87, 85, 89, and 82μM. IC50 values 100–150μM. compound 12 was inactive (IC50 > 200μM).	(Peng et al., 2013)

N Tosylindole (4a), N Tosyl-6-bromoindole (4b), N Tosyl-3-acetylindole (5a), N Tosyl-3 6 bromoindole (6b), 3-Cyano-6-bromoindole (7b), N-Tosyl-3-cyanoindole (8a), cyano bromoindole (8b), N Hydroxy bromoindol formamidine (9b), N-Hydeoxy-p metoxybenzamidine (9e), N-Hydeoxy-thiophene-3 formamidine (9f),	*Sponosorites ruetzleri*	sponges	Extracted with Ethyl acetate	TMV , Mythimna separate, Helicover armigera, Candida albicans,	cc50 values: 2e- 59% 2k- 58% showed greater antiviral activity. Compounds 1f, 2h, 2m-higher. Compounds2e,2k- high antiviral activity.	(Ji et al., 2018)

N Hydeoxy-hendecylamidine (9g), N Tosylindole 3formamidine (10a), N Tosyl-6-bromoindole-3 formamidine (10b), 4 Methoxybenzimidamide acetate (10e), Thiophene-3-carboximidamide acetate (10f), Hendecylamidine (10g), N,N′Ditosylnortopsentin D, N,N′-Ditosylnortopsentin B (2b), N,N′-Ditosylnortopsentin C (2c),						

Nortopsentin D (1a). Nortopsentin B (1b), Nortopsentin C (1c), Nortopsentin A (1d)						
Melicopteline A, Melicopteline B, Melicopteline C, Melicopteline D, Melicopteline E	*Melicope pteleifolia*	Leaves	EtOAc extraction method	H1N1 and H9N2 influenza A viruses in MDCK cells.	IC50 values: Melicopteline A - 5.43 ± 2.32 Melicopteline B - 4.75 ± 1.39 MelicoptelineC- EC50 value- 2.57 ± 0.45μM (most potent) Melicopteline D - 3.70 ± 0.25 μM Melicopteline E - 4.28 ± 2.41 μM ribavirin EC50 value- 3.92 ± 0.79μM MelicoptelineC, MelicoptelineD, MelicoptelineE exerted more potent activity. Among them, Melicopteline C demonstrated greater selectivity and substantially higher activity (EC50, 2.57 ± 0.45 μM) than the positive control ribavirin (EC50, 3.92 ± 0.79 μM).	(Lee et al., 2021)
Harman,	*Commelina commun*	Leaves,	Compounds were isolated	influenza A, A/PR/8/34	CC_{50} values: harman 240.8	(G. B. Zhang et al., 2013)

homonojirimycin (HNJ), 2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine	*is L. (TAC)*	stem,root,	from TAC by HPLC(column)/CPE reduction	virus (H1N1).	HNJ 186.0 DMDP 94.3 Ribavirin 325.8 EC50 b (µg/mL) : harman 68.9 HNJ 10.4 (STRONG) DMDP 121.5 Ribavirin 15.2 SI values: harman 3.5 HNJ 17.9 DMDP less than 1 Ribavirin 21.5	
1.Pimprinine 2. 5oxazole 3. 5 oxazole 4.5-2-isopropyloxazole 5.Labradorin 1 6.2-Cyclohexyl-5oxazole 7.5oxazol-2-yl)methanol 8.5oxazole 9.5phenyloxazole 10.2oxazole 11.Pimprinaphine 12.4oxazolphenol 13.2-Methyl-5 oxazole	Streptomyces pimprina	Leaves, bark, root.	filtrate	TMV	The EC50 Against TMV: 4phenol-211µg/mL 3carbohydrazide-290µg/mL 10h – 180µg/mL Ribavirin -694 Ningnanmycin- 203 Higher antiviral activities >ningnanmycin- 5l, 9h, 10h.	(B. Liu et al., 2019)

14.5 methyloxazole 15.Benzylidene 16. 3carbohydrazide						
Lycorine AA1, hippeastrine AA2 , hemanthamine AA3, 11-hydroxyvittatine AA4.	*Lycoris radiata*	bulbs	chromatographic methods	Avian influenza virus (AIV), type A, chicken, GuangDong, 178, 2004. (H5N1, 178)	EC90 value: oseltamivir and AA1–AA4 compound: Oseltamivir- 0.625 ± 0.11, μg/mL COMPOUND AA1-0.52 ± 0.57, (stronger antiviral activities) COMPOUND AA2-82.07 ± 0.33, μg/mL COMPOUND AA3- 4.15 ± 0.052, (stronger antiviral activities) Compound AA4- 13.45 ± 0.57μg/mL	(He et al., 2013)
Tetrandrine, (TET) Fangchinoline, (FAN) Cepharanthine, (CEP)	*Stephania tetrandra*	herbs	Alcohol Extraction	Coronavirus OC43 Infection of MRC5 Human Lung CELLS, CHCoV-OC43. herpes simplex, dengue, and Ebola.	IC50 values: TET0.33 ± 0.03μM FAN- 1.01 ± 0.07μM CEP -0.83 ± 0.07μM,	(Kim et al., 2019)
10-Hydroxyusambarensine C1, Strychnopentamine C3, Cryptoquindoline C2,	*Strychnos usambarensis*	Herb	-	SARS-Cov-2 RdRp..	SARS-CoV-2 RdRp binding affinities of –7.9 and –7.2 Kcal/mol	(Ogunyemi et al., 2020)

isocryptolepine, C8, millettosin, oryzanol C, usararotenoid A C4, remdesivir SI, sofosbuvir S2, Cinnamaldehyde, Thymoquinone, 12a epi-millettosin (C5), 24-Methylene cycloartenol (C6), Ekeberin C1 (C7), Dioncophylline B (C9), Usararotenoid C (C10)						
Dragmacidin F Dragmacidin D	*Halicortex sp.*	leaves, root, bark, stem.	Ethanol extract	Hiv Hsv	EC50 VALUES: Dragmacidin F – 95.8 μM (HSV) -0.91 μM (HIV) Dragmacidin D – HSV - 95.8 μM Hiv- 0.91	(Cutignano et al., n.d.)
1.protopine 2.beta-allocrypto-pine, 3. benzylisoquinoline-4.(+)-norjuziphine, 5.benzophenanthri-dine-type [sanguinarine, 6.norsanguinarine,	*Fumariace plant* *Fumaria L.* , *Corydalis medik.* .	Leaves , root	EtOH Extract	DNA virus Herpes simplex (HSV), RNA virus Parainfluenza 3 virus (PI-3), Escherichia coli, Pseudomonas aeruginosa,	CC50 values- Protopine- 32% (PI3) Beta-allocryptopine – 32% PI3 Fumarophycine acetate – 32 % Corporationine -32% Sibiricine – 32% sibiricine acetate -32% Dihydrosibiricine -32% Bicuculline- 64% Adlumidine-32% 128% canadine 32% sinactine Ophiocarpine-64	(Orhan et al., 2007)

7.chelidimerine, 8.spirobenzylisoquinoline 9.(Đ)-fumarophycine acetate, 10.(Đ)-corpaine , 11.(ð)-sibiricine 12.sibiricine acetate, 13.(ð)-dihydrosibiricine, 14.(+)-fumariline, 15.(Đ)-dihydrofumariline, 16.(+)-parfumine, 17.parfumine acetate, 18.(Đ)-dihydroparfumine diacetate], 19.phthalide-isoquinoline 20.(+)-bicuculline, 21.(Đ)-bicuculline, 22.(Đ)-adlumidine 23.[(+)-bulbocapnine, 24.(+)-isoboldine, 25.berberie, 26.stylopine, 27.canadine, 28.sinactine, 29.ophiocarpie 30.ophiocarpine-N-oxide ,				Proteus mirabilis, Klebsiella pneumoniae, Candida albicans, Acinetobacter baumannii, Staphylococcus aureus, and Bacillus subtilis	ophiocarpine-N-oxide-64% corydalmine -64% Palmatine-32%	

31.corydalmine 32.palmatine 33.(ð)-corydalidzine, 34.dehydrocorydaline 35.dehydrocavidine, 36.(+)-cularicine, 37.oxocularine, 38.oxosarcocapnine 39.oxosarcocapnidine, 40.corydaldine.						
1.8,14-DIHYDROAMURINE, 2.-MECAMBRIDINE, 3.ALBORINE, 4.8,14-DIHYDROFLAVINANTINE, 5.–FLAVINANTINE, 6.-AMURENSINE 7.– O-Methylarmepavine 8.-Mecambridine methohydroxide	*Papaver pseudocanescens M.*	Air dried and ground aerial parts	EtOH	HRV-14, CV-B1, HRSV-A2, HAdV-5, POLIVIRUS-1.	Cytotoxicity CC50 values [μM]: HeLa cells: 1. 8,14-DIHYDROAMURINE- 166 μM 2. MECAMBRIDINE-174 μM 3. ALBORINE- >200 μM 4. 8,14-DIHYDROFLAVINANTINE- 378 μM 5. – FLAVINANTINE- 207 μM 6. - AMURENSININE- 273 μM 7. – O-Methylarmepavine- 151 μM 8. -Mecambridine methohydroxide - >200 μM -Mecambridine methohydroxide gives the most promising effect	(R. Istatkova et. Al., 2012)

					with selectively index ecceding	
Anisomycin	*Streptomyces Griseolus*	Bacteria	MTS Colorimetric assey	Dengue virus (DENV), DENV NS5, (DENV -1-2, -3, -4,), Zika virus.	EC_{50} Value of Anisomycin – 1.4 micro M.	(Quintana et al., 2020)
Berberine	*Berberis Vulgaris L.*	Non toxic plant parts	Colorometric method	Chikunguny a virus (CHIKV), HEK- 293T	CC_{50} of HEK- 293T Berberine- 202.6 microM $EC_{50\ OF}$ LR2006 OPY1 – 37.6 SGP11-44.2 CNR20235- 50.9 (these are diff. strains of CHIKV)	(Varghese et al., 2016)

Table 1 : Antiviral alkaloids results, extraction method, pathogens they work against and parts.

4.3 Chemical Structures

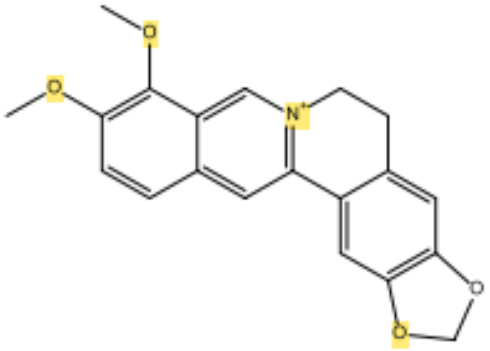


Figure: Berberine (Guo et al., 2019).

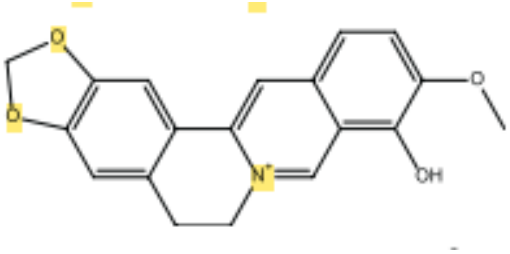


Figure: berberrubine (Guo et al., 2019).

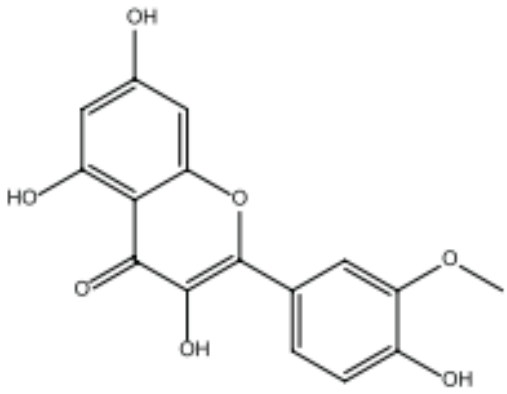


Figure: Isorhamnatine (Guo et al., 2019).

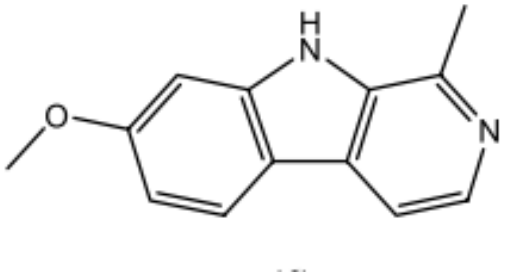


Figure: Harmine (Hegazy et al., 2023)

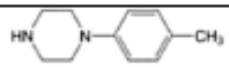
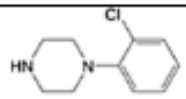
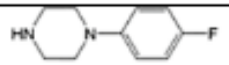
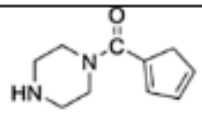
No.	R1	R2	R3	Activity	Reference
1		-OH	-	Anti-influenza	Enkhtaivan et al., 2017 [67]
2		-OH	-	Anti-influenza	Enkhtaivan et al., 2017 [67]
3		-OH	-	Anti-influenza	Enkhtaivan et al., 2017 [67]
4		-OH	-	Anti-influenza	Enkhtaivan et al., 2017 [67]
5	-	$-CH_3$	$-CCl_3$	Anti-human cytomegalovirus (HCMV)	Hoyashi et al., 2007 [81]
6	-	$-CH_3$	-CN	Anti-human cytomegalovirus (HCMV)	Hayashi et al., 2007 [81]
7	-	$-CH_3$	-H	Anti-human cytomegalovirus (HCMV)	Hayashi et al., 2007 [81]

Table 2: Antiviral Berberine derivatives (Warowicka et al., 2020).

4.4 Herbal medicines in covid19 treatment

4.4.1 Herbs

Eight different studies were included in our analysis to see how herbs affected COVID-19 patients. Six of the studies involved herbal formulations, and the other two focused on single herbs used by themselves. According to the results of three randomized controlled trials (RCTs) completed in 2020, the Lianhua Qinwen tablet seems to have the potential to boost the rate of symptom recovery among COVID-19 patients. These trials were conducted in 2020. During a two-week randomized controlled trial, the effects of adding four Lianhua Qingwen capsules three times daily to the standard treatment recommended by the diagnosis and therapy Guidelines for Covid Pneumonia 2020 were compared to the effects of administering the standard treatment alone in the control group (RCT) (Feng et al., 2021). As a result of demand being driven by COVID-19-related herbal use, such as supposed immunological health and stress reduction, the herbal market achieved a new high in 2020, expanding by 17.3% in comparison to the previous year. This was an all-time high for the herbal industry. This represented very first time that the herbal business experienced double-digit growth. Over the course of the past two decades, annual sales of herbal supplements have steadily increased, culminating in record-breaking spending of $11.261 billion in 2020, which is $1.659 billion more than was spent in 2019 (Hassen et al., 2022).

4.4.2 Global and US Herbs Consumed

4.4.2.1 (ABC)

Wheatgrass/Barley grass, Elderberry, Horehound, Cranberry, Turmeric, Apple Cider Vinegar, Ginger, Echinacea, Garlic, Fenugreek, Ashwagandha, saw palmetto, and Green tea, Ivy leaf, Ginkgo, Aloe, Black cohosh, Red yeast rice, Cannabidiol (CBD), Black cohosh, Flax oil and flax seed, horny goat weed, milk thistle, yohimbe, goji berries, valerian, bioflavonoid complex, Green coffee extract, Senna, Beetroot, Cinnamon, Plant Sterols, Rhodiola, Ginseng, Chamomile, Garcinia, Fennel, Maca (Hassen et al., 2022).

4.4.2.2 (NIH)

Acai, Astragalus, Aloe Vera, Asian Ginseng, Bilberry, Bitter Tangerine, Black Cohosh, Chamomile, Chasteberry, Cinna, Cranberries, Chamomile, Juniper berry, Ephedra, European Mistletoe, Evening, Echinacea, Elderberry, Evening Primrose, Primrose Oil, Fenugreek, Feverfew, Flaxseed and Flaxseed Oil, Garcinia Cambogia, Garlic, Green Tea, Grape Seed, Mugwort, Peppermint Oil, Pomegranate, Clover, (Hassen et al., 2022).

4.5 Herbal Medicine for Cough

A disease such as an upper respiratory tract infection (URTI) or the common cold or exposure to smoke or allergens in the environment in the surrounding area are the most prevalent causes of the symptoms of an acute cough. Only a select few of these therapy modalities, including phytotherapies, hydrotherapies, and Traditional Chinese Medicine (TCM), are utilized in mainstream medicine, although herbal medicines are one component of a wide-ranging spectrum of treatments that are available. Alternative medicine also makes use of medicinal plants in the form of herbal remedies. Although though herbal treatments have a long history of use in many different cultures, there is frequently a dearth of data on their efficacy from randomized controlled trials (RCTs). Ivy, primrose, and thyme-based medicines are some of the herbal cough therapies that have been shown to be effective in clinical trials. These preparations are indicated as expectorants in the most recent European guidelines (Wagner et al., 2015).

4.6 HERBAL MEDICINE IN CANCER TREATMENT

The anticancer drug emodin also has immunomodulatory effects on the immune system. This is accomplished by breaking the feedback loop that exists between macrophages and breast cancer cells and is responsible for boosting the growth of tumours. As a consequence, both the cells' proliferation and their ability to metastasize are inhibited. (Luo et al., 2019). Combination therapy is frequently employed to improve efficacy of beta elements in cancer therapy (Luo et al., 2019).

4.6.1 Treating Breast Cancer

One of the main causes of death for women globally is breast cancer. Radiation therapy (RT), surgery, endocrine therapy (ET), chemotherapy (CT), and targeted therapy are among the treatments that are currently accessible. Due to their little to nonexistent adverse effects, these treatments come with side effects that necessitate the use of natural drugs. Such a group of chemical compounds is the alkaloids. Due to their potential therapeutic uses, alkaloids are a class of naturally occurring compounds that have garnered a lot of attention. In addition to having antibacterial characteristics, alkaloids also have antiviral and anti-inflammatory activities. Every species of barberry contains the two key compounds berbamine and berberine. Berberine and berbamine, two alkaloids, both have anticancer effects. It has also been observed that berberine blocks the cell cycle during the G1 or G2/mitosis/meiosis (M) phase. Berberine's anti-cancer action efficiently slows the cell cycle. (Rampogu et al., 2022).

4.7 P. hamala

Seeds of the P. harmala plant have been used as a herbal treatment for millennia. According to reports, P. harmala contains antibacterial, antiviral, and antiplasmodial activities. Anti-influenza virus activity of P. harmala seed extract has not been reported to our knowledge. In this study, the antiviral activity of P. harmala seed extract was evaluated by inhibiting viral RNA transcription and replication in MDCK cells. In the current study, the crude extract inhibited the replication of the influenza A PR8 virus in this cell line, with an IC50 value of 9.87 (CI95%: 7.3-11.3) g/ml and a SI value of 12.2. Using further antiviral assays that examined the titers of HA or infectious viral particles in the culture supernatants, in addition to the viral RNA and viral protein levels in the cell lysates, it was determined that the crude extract of P. harmala seed may prevent influenza virus generation. Given that the IC50 value

of a typical herbal extract against infectious diseases is less than 100 g/ml, this extract, with an IC50 of 9.87, could have potent anti-influenza virus activity. This extract's total alkaloids displayed antiviral activity, with an IC50 value of around 5.8 (CI95%: 3.7-8.9) g/ml and a SI value of 23.1, which was superior to that of the crude extract (M. T. Moradi et al., 2017).

4.8 Isoquinoline Alkaloids

Fumaria L. and Corydalis Medik are known to produce isoquinoline alkaloids derived from phenylalanine and tyrosine. In one study (Iwasa et al., 2001), the antibacterial, cytotoxic, and anti-HIV activities of 26 simple isoquinolines and 21 benzylisoquinolines were examined, and the isoquinoline- or dihydroisoquinoline-type quaternary nitrogen atoms It was found that antibacterial activity and cytotoxic efficacy could be enhanced. On the other hand, anti-HIV activity was higher with tetrahydroisoquinoline (Orhan et al., 2007). Numerous antibacterial, antiviral, antitumor, antimalarial and cytotoxic studies have been reported on various derivatives of natural isoquinoline alkaloids (Orhan et al., 2007).

4.9 Zika virus resistance (antiviral activity)

The viral titration was determined using the standard TCID50 method and was represented as log10 TCID50/mL. The day before to titration, vero cells were cultivated at a density of 1.104 cells per well in 96-well plates at 37°C and 5% CO2. Prior to addition, the cells received cell supernatants from the cytopathic effect assay that had been serially diluted 10 times in DMEM. The cells were then incubated for an additional five days at 37°C and 5% CO2. After that, an inverted optical microscope was used to assess the cytopathic effect. The TCID50 is computed

using the Reed and Muench, 1938 method, and the CPE is determined for each well. The TCID50/mL log10 scale was used to express the viral titer decrease (da Silva et al., 2021).

4.10. β-Carboline Alkaloids

B Carboline alkaloids, a fascinating side of indole-containing naturally found and manmade heterocyclic compounds dispersed widely. Due to their various biological actions, these alkaloids have garnered more attention in recent years. β -carbolines and similarly related artificial ingredients, with 73 natural instances. This discipline of alkaloid chemistry has clearly seen a proliferation of new and original synthetic routes, as well as inventive approaches for the synthesis of the title framework, over the last five years. Organic chemists are interested in the used processes and produced compounds because they have a high therapeutic potential. This review is inspired by the critical need for innovative medication candidates, which is driving the highlighted development (Szabó et al., 2021).

4.11 The Importance of Herbal Supplements and Their Impact on Clinical Practise

Among the most frequently cited reasons for using natural product supplements for wellness purposes among U.S. adults in 2012 were general wellness or disease prevention (83.3%), improving immune function (42%) and improving energy (31%), focusing on the whole person (mind, body, and spirit) (26.5%), and improving memory or concentration (22%).. In addition, focusing on the whole person (mind, body, and spirit) was among the most frequently cited reasons for using natural product supplements. Herbal supplements, despite their natural origin, have been linked to a variety of adverse health effects and side effects, some of which are

considered to be harmless. These adverse health effects and side effects are the result of physiologically active herbal ingredients, pollutants, and interactions between herbs and pharmaceuticals (HDI).

Nationally representative surveillance data of 3667 cases obtained from 63 emergency departments in the United States and analysed for 2004-2013 visits estimated that 23,005 annual visits in the United States were attributable to negative effects connected to DS. These visits resulted in an estimated 2,154 annual hospitalisations (95% CI: 1,342-2,968). When used for weight loss (25.5%; 95% CI: 23.1-27.9) and enhanced energy (10%; 95% CI: 8.0-11.9), herbal or supplemental nutritional goods were commonly related with adverse events such as palpitations, chest pain, or tachycardia (71.8%; 95% CI: 67.6-76.1) (Hassen et al., 2022).

4.12 Alkaloids

There is a wide variety of alkaloid structures, metabolic processes, and pharmacological actions. Alkaloids belong to the most diverse groups of secondary metabolites discovered in living organisms. Alkaloids have typically been isolated, in the majority of cases, from plants. Furthermore present in a wide variety of species, including mammals, insects, marine invertebrates, and microbes. There are many alkaloids that have been used in medicine for the past few hundred years, and some of these alkaloids are still widely utilized today. Since these chemicals have been utilized as medications in potions, medicines, teas, poultices, and poisons over the past 4,000 years, human recognition of alkaloids is at least as ancient as civilization itself.

Alkaloids are a type of nitrogenous chemical substances derived from plants that exert profound physiological effects on humans. True alkaloids, protoalkaloids, and pseudoalkaloids are the three primary types of alkaloids. True alkaloids and protoalkaloids are generated from

amino acids, whereas pseudoalkaloids are not. True alkaloids are alkaloids that are derived from amino acids and share a ring which is heterocyclic by structure containing nitrogen. They have a high degree of reactivity and biological activity by nature. Several of them are crystalline in nature, which conjugates with an acid to produce a salt. The N atom produced from an amino acid is absent from the heterocyclic link in protoalkaloids. These alkaloids include l-tyrosine and l-tryptophan-derived compounds. Protoalkaloids are alkaloids with a closed ring that are structurally perfect but simple. Any substance with alkaloid-like properties that is not derived from amino acids. Caffeine is an example of a pseudoalkaloid. A few alkaloids lack the distinctive carbon structure of their group. Thus, homoaporphines and galanthamine do not include isoquinoline fragments, but they are typically classified as isoquinoline alkaloids. Herbal treatments have been utilised for the prevention and treatment of numerous diseases since the dawn of time. In general, it is believed that the risk associated with herbal medications is minimal; however, reports of severe reactions indicate the need for the development of effective marker systems for isolating and identifying the specific components. Globally, standards for herbal medicines are being created, but there is still no agreement regarding how they ought to be applied. Herbal medication standardization, stability, and quality control are possible but challenging to implement. Also, different nations have different laws governing these medications. Several approaches are taken by different medical systems and nations to achieve stability and quality control. The current study aims to determine the development of regulatory guidelines for the commercialization of herbal pharmaceuticals as well as the advancement of technical standards in manufacturing (Sahoo et al., 2010).

4.12.1 True Alkaloids

Alkaloids can largely be categorised based on where they come from and how they are made. In accordance with the source of their development, the alkaloids can be broken down into one of three distinct groups: true alkaloids, protoalkaloids, or pseudoalkaloids. The heterocyclic rings that include nitrogen can be found on the real alkaloids, which originate from amino acids (Rampogu et al., 2022).

4.12.2 Protoalkaloids

The nitrogen group that is often found in protoalkaloids, which are formed from amino acids, is absent from the heterocyclic ring in which they are contained (Rampogu et al., 2022).

4.12.3 Pseudoalkaloids

Pseudoalkaloids are heterocyclic rings with nitrogen in them, but they do not originate from amino acids. They use transamination to introduce the nitrogen group (Rampogu et al., 2022).

4.12.4 Further Classification

The alkaloids are also subdivided according on their ring structure. The piperidine, which has a C5N nucleus and a unique flavor, is the primary ring of piperidine alkaloids. (Rampogu et al., 2022)

Chapter 5

Findings and Discussion

This research review needed more than 120 articles, case reports, and clinical opinions that describe or contribute to our understanding of the antiviral activity. of the naturally occurring alkaloids. In the analyses, we have made the following topics clear:

- Naturally found alkaloids showing antiviral effects
- Their source of plant, name and the extraction method
- Pathogens they worked against
- Mechanisms of action, Results and Comparisons

Herbal medicines are well-known for their potent antiviral properties against a variety of viruses that cause viral infections. Antiviral drugs aid the body in warding off harmful viruses. The medicines can shorten the duration of a viral infection and reduce its symptoms. There are numerous naturally occurring alkaloids with antiviral properties. To lower the prevalence of these viral illnesses, it is crucial to identify alkaloids present naturally in plants that have antiviral properties and that is what has been done on this study. Natural phytochemicals known as alkaloids have been widely investigated for their wide range of antiviral effects against various DNA and RNA viruses. Alkaloids are renowned for their biological activities. They are crucial for both human health care and an organism's natural defense. Many alkaloids derived from natural herbs have demonstrated in vitro and in vivo antiproliferation properties, antibacterial, antiviral, insecticidal, and antimetastatic properties on different forms of cancer. There is a diverse range of pharmacological effects that can be caused by alkaloids, including such quinine, which has antimalarial properties, ephedrine, which has asthmatic properties,

homoharringtonine, which has anticancer properties, galantamine, which is cholinomimetic, vincamine, which is vasodilatory, quinidine, which has antiarrhythmic properties, and morphine, which has analgesic and antibacterial properties. The plant sources are well easy to find and the extraction methods are as usual to use which makes the study more relevant to apply in the present days as well as in the near future to overcome such viral diseases. All of the alkaloids included in the study have shown significant antiviral activity against the mentioned viruses.

Chapter 6

Limitations of the Study

There are significant constraints on our research that we should have accounted for. Traditional Persian medicine makes use of a wide variety of medicinal herbs, many of which have shown to be effective in the treatment of neurological disorders (Moradi et al., 2020). Despite having several benefits, there are also some drawbacks. The merging of integrated medicine with current science is thought to eventually aid in the treatment of degenerative disorders. In spite of the substantial progress made in the management of neurological disorders, there are still several restrictions and impediments that need to be addressed (Moradi et al., 2020). Not all biological activities and mechanisms are discovered. Additionally, additional study regarding the antiviral characteristics and mechanisms of all alkaloids should be conducted to ensure the optimal amount. Similarly, not all publications were found to provide all the necessary material for proper study. Certain alkaloids were administered without the required mechanisms. Uncertainty surrounded certain comparison group results for all outcomes (Zhou et al., 2021). The certainty of the evidence was perceived to be diminished. The primary shortcomings of the evidence were the absence of evidence for all processes or adverse outcomes, inadequate description of study methodologies, and imprecision due to low occurrence rates and broad confidence ranges.

Chapter 7

Conclusion

This study delineates the antiviral properties of naturally occurring alkaloids that are derived from plants and extracted utilizing several extraction techniques. One of the major problems that the world is currently dealing with in this century is viral infections. There are numerous naturally occurring alkaloids, which result in very simple-to-make herbal medicines. The results against numerous viral infections that pose a threat to life are quite positive. In light of this finding, it is crucial to expand the usage of these herbal medicines in order to protect against viral illnesses. Future research may focus on additional in-depth information on this to better comprehend the implications of the results. Herbal medications are crucial in the battle against such dangerous viral diseases. Additionally herbal medicines demonstrating their antiviral effects, despite there being some debates about their use and appropriateness.

7.1 Future research plan:

We can concentrate on a small amount of study opportunities in the future. First, let's discuss the connection between alkaloids and the disorders they can treat. Secondly, Further study into the mechanisms of the alkaloids thoroughly . Furthermore, extensive study should be undertaken on naturally occurring alkaloids with antiviral properties in an effort to develop therapy options using alkaloids that are more focused and suitable for all individuals in need of therapies.

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