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Contents

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Research Article

Evaluation of Release Kinetics of Some Marketed Controlled or Sustained Release Tablet Preparations of Theophylline Using Their Dissolution Profile.

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ABSTRACT

Theophylline, a methylxanthine derivative, found in tea with diuretic effect, is indicated mainly for asthma, bronchospasm and chronic obstructive pulmonary disease (COPD). As it is a narrow therapeutic index drug requiring determination of its release kinetics. In this study, in-vitro dissolution tests were performed to predict the release behavior of controlled release theophylline oral tablet of five Bangladeshi brands using renowned mathematical models. The release kinetics of all the marketed tablets are best fitted with the well-known, polymeric system suitable exponential Korsmeyer- Peppas equation as the plots showed high linearity with regression value of 0.996, 0.999, 0.997, 0.993 and 0.998 for all the five samples. Here release mechanisms are found to be non-Fickian type of diffusion expressing drug release by combination of both diffusion and erosion-controlled rate release, as they showed release exponent value of 0.59, 0.57, 0.60, 0.54 and 0.58 for TP-1, TP-2, TP-3, TP-4 and TP-5 respectively. Similarly the dissolution data of all investigated tablets was also fitted to the Higuchi's square root equation, as the plots showed good linearity with regression value of 0.990, 0.993, 0.994, 0.998 and 0.995 for TP-1, TP-2, TP-3, TP-4 and TP-5 respectively, indicating that the drug releases follow the Higuchi release kinetics, and diffusion is the dominating drug release mechanism of controlled/sustained release theophylline tablets.

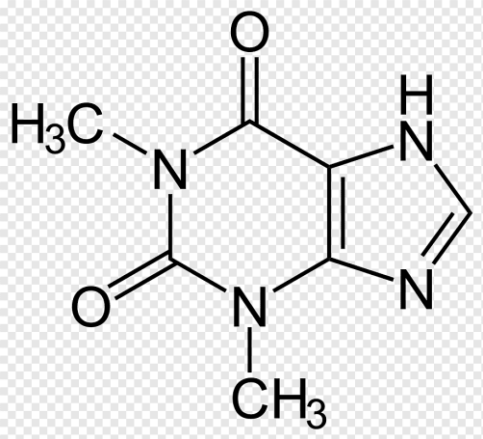
Keywords: Theophylline, Korsmeyer-Peppas equation, Higuchi's equation, controlled/sustained release, mathematical models.

INTRODUCTION

Theophylline is, a methylxanthine derivative, very effective in the chronic treatment of bronchial asthma, bronchospastic reactions and chronic obstructive pulmonary disease (COPD).[1] It bears structural and pharmacological similarity to caffeine. The mechanism of

action of this drug is to cause antagonism at the adenosine receptor binding site.[1,2]Theophylline is a non-specific adenosine antagonist, which explains many of its cardiac effects and some of its anti-asthmatic effects.[1] Another proposed mechanism of action includes a non-specific inhibition of phosphodiesterase enzymes, producing an increase in intracellular cyclic AMP.[3,4] Its therapeutic concentration range is narrow (from 10 to 20 µg/ml) while toxicity usually appears at concentrations above 20 µg/ml and the fluctuations of its serum concentrations can result in variability in clinical response.[1] It is quickly absorbed and eliminated with a plasma half-life of 6 to 8 hours and t_{max} of 1 to 2 hours. As it is a narrow therapeutic range drug it may require drug monitoring both to achieve therapeutic levels and to minimize toxicity.[1,3] Again tablets are widely prescribed and accepted oral dosage form offering advantages like unpleasant taste masking, accuracy of dose, ease of administration, protection of drug against temperature, humidity, oxidation, photodegradation and stress during transportation.[2] But conventional tablet formulations are not ideally suited to some drugs having short plasma half-life, high absorption rate and narrow therapeutic index.[1,3] In order to meet all these issues, sustained or controlled release tablets of theophylline seems to be the most appropriate dosage forms.[4,5,6] Also these types of products are designed to maintain constant therapeutic plasma concentration of the drug within the therapeutic range over prolonged periods of time.[7] The effectiveness of such delivery system is increased due to reduced frequency of dosing, minimizing dose and side effects.[8,9] So modern pharmaceutical studies have focused on controlled drug delivery which has an advantage over conventional approaches.[8] Adequate controlled plasma levels, reduced side effects, as well as better patient compliance are some of the benefits that these systems may offer.

On the other hand mathematical models play a vital role in the interpretation of mechanism of drug release from a dosage form.[11,12,13] These are the important tools to understand the drug release kinetics of different pharmaceutical preparations.[2,3] The present study was undertaken with an aim to assess the mechanistic kinetics of drug release of some marketed controlled release tablets of narrow therapeutic indexed theophylline by using dissolution test profiles and different renowned mathematical models.



Theophylline structure

MATERIALS AND METHOD

Materials

Collection of Sample:

Sustained or controlled release Theophylline oral tablet samples of five Bangladeshi Pharmaceutical companies were purchased from commercial lots currently available in the local market. The samples were coded as TP-01, TP-02, TP-03, TP-04 and TP-05.

Some particulars of the same are tabulated below:

Table 1: List of controlled/sustain release theophylline oral tablet brands with code and composition.

Name of the company	Brand name	Abbreviated name	Composition
Square Pharmaceuticals Ltd.	Contifil	TP-01	Each tablet contains theophylline BP 400 mg.
Incepta Pharmaceuticals Ltd.	Arofil SR	TP-02	Each tablet contains theophylline BP 400 mg.
Aristopharma Ltd.	Contine	TP-03	Each tablet contains theophylline BP 400 mg.
Drug International Ltd.	Theovent SR	TP-04	Each tablet contains theophylline BP 400 mg.
Opsonin Pharma Ltd.	Unilin CR	TP-05	Each tablet contains theophylline BP 400 mg.

Standard:

Theophylline standard was collected from Gonoshasthaya Pharmaceuticals Limited, Savar, Dhaka, Bangladesh.

Methods

***In-vitro* Dissolution Studies:**

In-vitro dissolution studies were performed in 900 ml monobasic phosphate buffer solution of P^H 4.5. The temperature of the medium was maintained at 37± 0.5^0 C. The USP type II apparatus (paddle method) was used and rpm (rotation per minute) for each paddle was set to 75. After 1hr, 2hrs, 4hrs and 8hrs, a definite volume (10 ml) of aliquots from each sample were collected for analysis, which were then replaced with equal volume of buffer solution of P^H 4.5. The dissolution study was continued for 8 hours to get a simulated picture of drug release. The drug released at different time intervals was measured by a UV-visible spectrophotometer at 271 nm wavelength. These values of the drug released from each tablet were plotted in graphs of drug released versus time. For elucidation of the drug release mechanism, dissolution data were analyzed using zero order, first order, Higuchi, Korsmeyer-peppas and Hixson-crowell equations, with linear regression.

Preparation of dissolution medium:

For dissolution medium, buffer solution of P^H 4.5 was required.

Preparation of buffer solution:

For buffer solution, 6.8 gm of monobasic Potassium dihydrogen phosphate was dissolved in sufficient distilled water to produce 1000 ml. P^H was adjusted to 4.5 by using 1N sodium hydroxide solution.

Preparation of Standard solution:

Take 10 mg raw material of theophylline in a 100 ml volumetric flask containing about 50 ml dissolution medium. Shake the solution to get the substance dissolved. Volume the solution up to the mark with the dissolution medium.

Then from the solution, take 5 ml in another 100 ml volumetric flask and dissolution medium added to volume up to the mark.

***In-vitro* Release Kinetics study:**

To study the release kinetics, data obtained from *in-vitro* drug release study were tested with different renowned mathematical models.

RESULTS AND DISCUSSIONS

Preparation of Concentration Vs Absorbance curve for the estimation of Theophylline content in the dissolution medium.

Accurately weighed 10 mg of theophylline RS was transferred into 100 ml volumetric flask and dissolved in small quantity of dissolution medium (phosphate buffer; P^H 4.5) and diluted up to the mark with dissolution medium to give a standard solution of 100 µg/ml. Further dilutions were made to produce 5 µg/ml concentrations with dissolution medium and absorbance was measured at 271 nm.

Drug release of theophylline from each tablet containing 400 mg of the drug was performed using dissolution apparatus II. The dissolution medium was 900 ml of P^H 4.5 phosphate buffer, kept at 37^0C and stirred at 75 rpm. Samples (10 ml) was taken from each tablet containing medium at specified time intervals (1 hr, 2hrs, 4hrs, 8hrs) and diluted in ratio (1:19), then replaced with fresh aliquots of the dissolution medium. After that each tablet samples were assayed for drug concentration after each specified time intervals by using UV spectrophotometer at 271 nm. Then concentration vs absorbance curve was prepared for each tablet plotting concentration at x-axis and absorbance at y-axis and it gives a straight line.

Table 2: Data for preparing Concentration VS Absorbance curve for each type of samples.

Time in Hours	TP-1		TP-2		TP-3		TP-4		TP-5	
	Conc.	Abs.	Conc.	Abs.	Conc.	Abs.	Conc.	Abs.	Conc.	Abs.
0	0	0	0	0	0	0	0	0	0	0
1	1.124	0.216	1.202	0.231	1.087	0.209	1.280	0.246	1.181	0.227
2	1.696	0.326	1.785	0.343	1.701	0.327	1.910	0.367	1.774	0.341
4	2.575	0.495	2.622	0.504	2.596	0.499	2.752	0.529	2.653	0.510
8	3.897	0.749	3.944	0.758	3.762	0.723	3.975	0.764	3.928	0.755

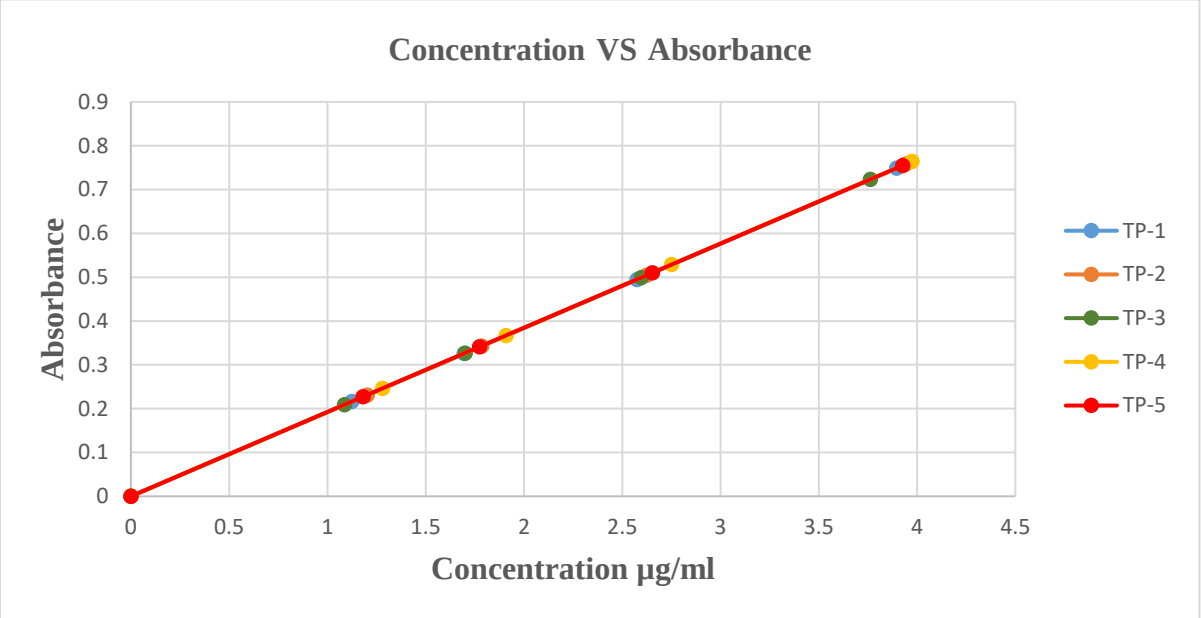


Figure 1: Calibration Curve for Theophylline

***In vitro* dissolution and release kinetics:**

In vitro release studies were carried out for all types of samples (TP-1 to TP-5) as per USP type II tablet dissolution tester employing rotating paddle at 75 rpm and using 900 ml of P^H 4.5 phosphate buffer medium for 8 hours. The release status of all types of samples is categorized in some particular co-ordinate fashion in order to understand their release behavior under same background but in multiple ways at the same time. The % drug release calculated from each tablet (TP-1 to TP-5) after specific times are converted to different variables to provide multiple data suitable for release characteristics that are established so far in

the field of controlled release dosage formulations.

Following release models were used for each branded tablet to find which one is suitable at appropriate manner-

- Zero order equation
- First order equation
- Higuchi release equation
- Korsmeyer- Peppas equation
- Hixson-Crowell release equation

All the tablet samples (TP-1, TP-2, TP-3, TP-4, TP-5) were taken for dissolution test and results obtained through UV-spectroscopic method were accumulated for interpreting through above mentioned mathematical models.

Zero Order Plot:

Table 3: Zero order release profile of five investigated controlled release tablets (TP-1 to TP-5) of Theophylline.

Time in Hours	Cumulative % of Drug Released				
	TP-1	TP-2	TP-3	TP-4	TP-5
0	0	0	0	0	0
1	5.058	5.409	4.8915	5.75955	5.3145
2	7.6882	8.0926	7.70885	8.6567	8.0421
4	11.3483	11.88825	11.76705	12.4815	12.0272
8	17.66525	18.1356	17.0588	18.0251	17.8087

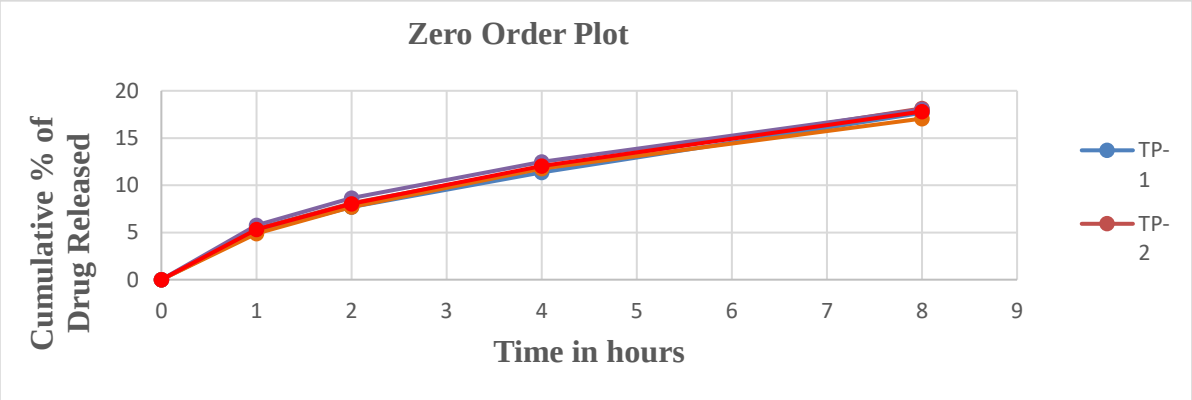


Figure 2: Zero order release profile of five investigated controlled release tablets (TP-1 to TP-5) of Theophylline.

Table 4: First order release profile of five investigated controlled release tablets (TP-1 to TP-5) of Theophylline.

Time in Hours	Log Cumulative % of Drug Remaining				
	TP-1	TP-2	TP-3	TP-4	TP-5
0	2	2	2	2	2
1	1.9775	1.9758	1.9782	1.9742	1.9763
2	1.9653	1.9634	1.9652	1.9607	1.9636
4	1.9477	1.9450	1.9456	1.9420	1.9443
8	1.9156	1.9130	1.9188	1.9137	1.9148

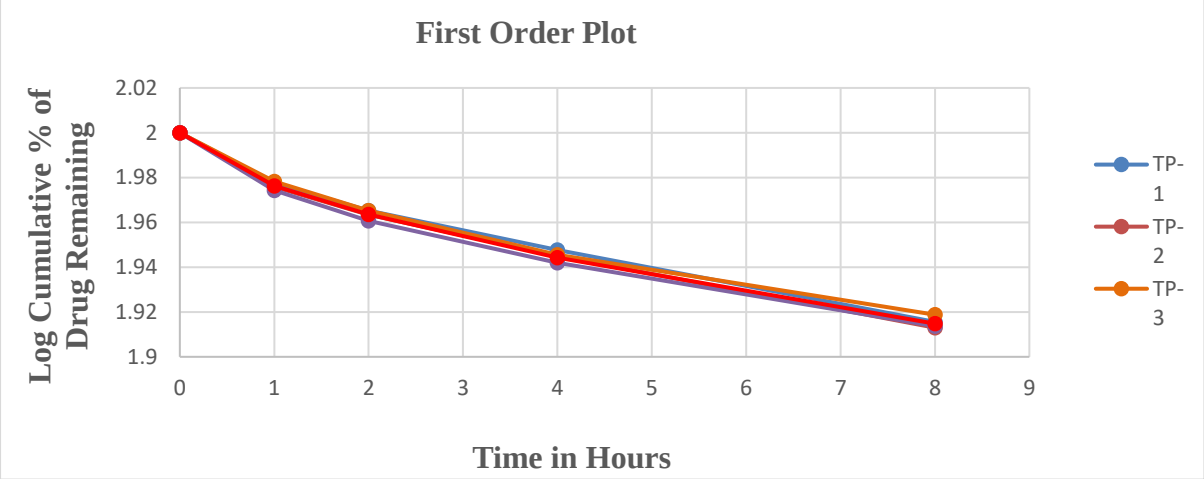


Figure 3: First order release profile of five investigated controlled release tablets (TP-1 to TP-5) of Theophylline.

Higuchi Plot:

Square Root of Time	Cumulative % of Drug Released				
	TP-1	TP-2	TP-3	TP-4	TP-5
0	0	0	0	0	0
1	5.058	5.409	4.8915	5.75955	5.3145
2	7.6882	8.0926	7.70885	8.6567	8.0421
4	11.3483	11.88825	11.76705	12.4815	12.0272
8	17.66525	18.1356	17.0588	18.0251	17.8087

Table 5: Higuchi release profile of five investigated controlled release tablets (TP-1 to TP-5) of Theophylline.

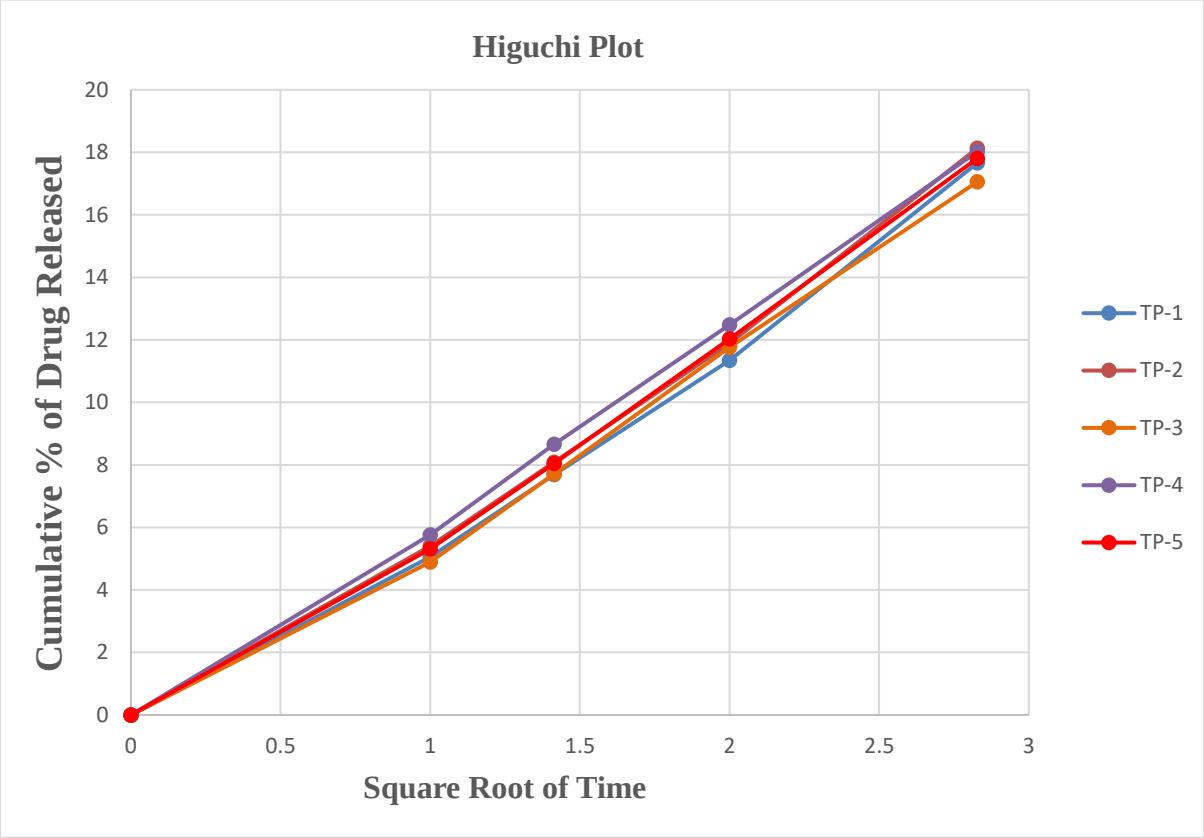


Figure 4: Higuchi release profile of five investigated controlled release tablets (TP-1 to TP-5) of Theophylline.

Korsmeyer-Peppas Plot:

Table 6: Korsmeyer-Peppas release profile of five investigated controlled release tablets (TP-1 to TP-5) of Theophylline.

Log of Time (hours)	Log Fraction of Drug Released				
	TP-1	TP-2	TP-3	TP-4	TP-5
0	-1.2960	-1.2669	-1.3106	-1.2396	-1.2745
0.30103	-1.1142	-1.0919	-1.1130	-1.0626	-1.0946
0.60206	-0.9451	-0.9249	-0.9293	-0.9037	-0.9198
0.90309	-0.7529	-0.7415	-0.7441	-0.7494	-0.7494

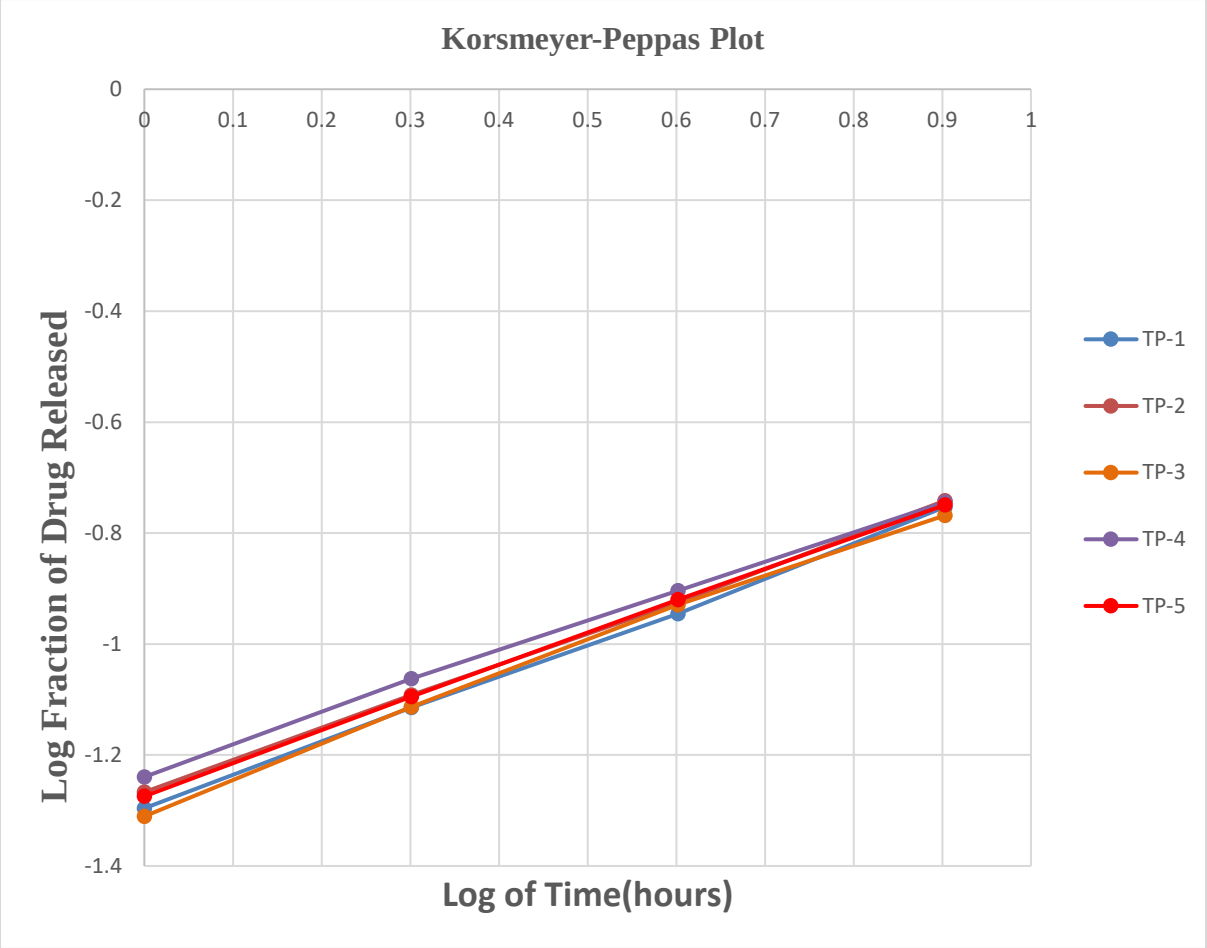


Figure 5: Korsmeyer- peppas release profile of controlled release tablets (TP-1 to TP-5) of Theophylline.

Hixson-Crowell Plot:

Table 7: Hixson-Crowell release profile of controlled release tablets (TP-1 to TP-5) of Theophylline.

Time in Hours	Cubic Root Total Amount of Drug (%) – Cubic Root Drug Remaining (%)				
	TP-1	**TP-2**	**TP-3**	**TP-4**	**TP-5**
0	0	0	0	0	0
1	0.0796	0.0852	0.0769	0.0908	0.0837
2	0.1221	0.1274	0.1225	0.1380	0.1279
4	0.1827	0.1917	0.1897	0.2018	0.1941
8	0.2911	0.2995	0.2805	0.2976	0.2937

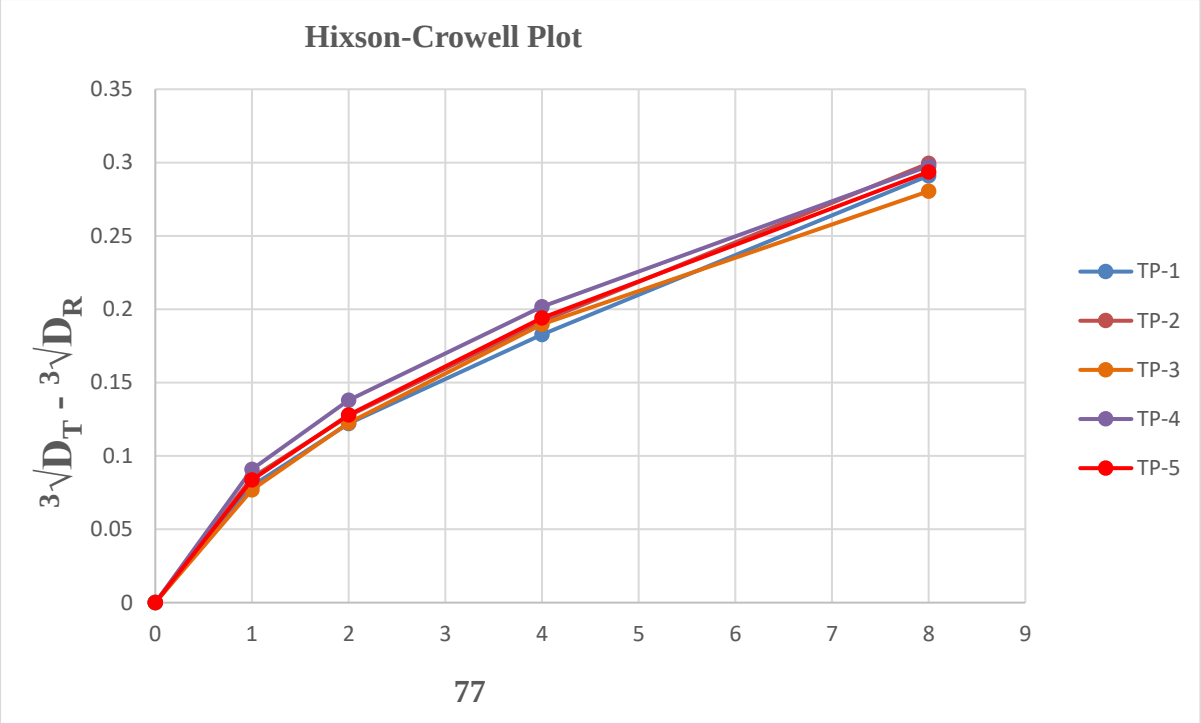


Figure 6: Hixson-Crowell release profile of five investigated controlled release tablets (TP-1 to TP-5) of Theophylline.

Interpretation of Release rate constants and Correlation Coefficient values for different release kinetics of TP-1 to TP-5.

Table 8: Release rate constants and correlation coefficient for different release kinetics of five investigated controlled release tablets of Theophylline:

Five Marketed Tablets	Zero Order		First Order		Higuchi		Korsmeyer-Peppas			Hixson-Crowell	
	K_0	R^2	K_1	R^2	K_h	R^2	K_{kp}	N	R^2	K_{HC}	R^2
TP-1	2.047	0.948	-0.00987	0.961	6.23	0.990	0.0505	0.59	0.996	0.034	0.96
TP-2	2.091	0.940	-0.01013	0.955	6.40	0.993	0.5398	0.57	0.999	0.035	0.95

TP-3	1.989	0.933	-0.00955	0.947	6.12	0.994	0.4990	0.60	0.997	0.033	0.94
TP-4	2.060	0.917	-0.00997	0.934	6.40	0.998	0.0583	0.54	0.993	0.034	0.92
TP-5	2.059	0.935	-0.00994	0.949	6.33	0.995	0.0534	0.58	0.998	0.034	0.94

The kinetic analysis of drug release of all the marketed tablets indicated that the most suitable models to describe the release kinetics of the tablet samples are the Korsmeyer- Peppas model and Higuchi release model.

As clearly indicated in **Table 08**, the investigated tablets showed to be best fitted to the well-known exponential equation, Korsmeyer- Peppas equation, as the plots showed high linearity with regression value of 0.996, 0.999, 0.997, 0.993 and 0.998 for TP-1, TP-2, TP-3, TP-4 and TP-5 respectively. This equation is often used to describe the drug release behavior from polymeric systems. According to Korsmeyer-Peppas equation, the drug release mechanism of all the tablets are found to be non- Fickian type of diffusion expressing drug release by combination of both diffusion and erosion-controlled rate release, as they showed release exponent value of 0.59, 0.57, 0.60, 0.54 and 0.58 for TP-1, TP-2, TP-3, TP-4 and TP-5 respectively.

The dissolution data of all investigated tablets was also fitted to the Higuchi's equation, as the plots showed good linearity with regression value of 0.990, 0.993, 0.994, 0.998 and 0.995 for TP-1, TP-2, TP-3, TP-4 and TP-5 respectively, indicating that the drug releases follow the Higuchi release kinetics, and diffusion is the dominating drug release mechanism.

CONCLUSION

The current work was to predict release mechanism of theophylline from the different investigated tablets by applying in vitro dissolution data into the different mathematical models.

The drug release mechanism of all the formulations was determined by fitting the in vitro release profile in various release kinetic models and the values of release exponent

(n), kinetic constant (K), and correlation coefficient (R^2) were determined.

The drug release of all the investigated formulations were found to be best fitted by Higuchi square root model and which implies that release of drug from tablets was diffusion controlled. Also, drug release followed Korsmeyer- Peppas Model, where n is the release exponent, indicating drug release by combination of diffusion of drug as well as erosion of tablet surface (non-Fickian diffusion). The result of the in vitro dissolution study indicated that all the marketed theophylline controlled/sustained released Bangladeshi tablets brand formulated using cellulose derivatives (e.g. hydroxyl propyl methyl cellulose, ethyl cellulose)[5,9] showed similar and well controlled drug release behavior.[8] The present study, although performed on a limited scale yet on the basis of professional judgement the data reported in this study can help Drug Control Authority to have an idea about the uniqueness of the marketed theophylline preparations in Bangladesh.

REFERENCE

1. Piper BJ, Alinea AA, Wroblewski JR, Graham SM, Chung DY, McCutcheon LR, Birkett MA, Kheloussi SS, Shah VM, Szarek JL, Zalim QK. A Quantitative and Narrative Evaluation of Goodman and Gilman's Pharmacological Basis of Therapeutics. Pharmacy. 2020 Mar;8(1):1.

2. ESCAP U. ESCAP publications 1998/1999.

3. U. S. P. Convention, USP 32 NF 27: United States Pharmacopeia [and] National Formulary. Volume 2, USA: United States Pharmacopeial Convention, 2009.

4. S. B. M. J. T. Bertram G. Katzung, Basic & Clinical Pharmacology, New York: The McGraw-Hill Companies, Inc, 2012.

5. M Asaduzzaman M, Rahman MR, Khan MS, Islam SA. Development of sustain release matrix tablet of ranolazine based on methocel K4M CR: in vitro drug release and kinetic approach. Journal of Applied Pharmaceutical Science. 2011 Oct 1;1(8):131.

6. Raja Sekharan T, Palanichamy S, Shanmuganathan S, Tamilvanan S And Thanga Thirupathi. Formulation and Evaluation of Theophylline Controlled Release Matrix. Ars Pharm. 2010.51(1) : pp. 28-38 .

7. "Wikipedia," Wikipedia, 16 November 2021. [Online]. Available: https://en.m.wikipedia.org/wiki/Theophylline.

8. M. A. Ege1, "Development and in vitro Evaluation of Theophylline," Indian Journal of Pharmaceutical Education and Research. 2016. 50(2).

9. Akter M, Banik S, Hossain MS. In vitro evaluation of oral extended release drug delivery system for metoprolol succinate using kollidon SR. Journal of Applied Pharmaceutical Science. 2012 May 1;2(5):188.

10. Wolny D, Gruchlik A, Chodurek E, Szara M, Dzierzewicz Z. Comparison of dissolution profiles of theophylline extended-release dosage forms. Acta Pol Pharm. 2012;69(6):13841386.

11. Gouda R, Baishya H, Qing Z. Application of mathematical models in drug release kinetics of carbidopa and levodopa ER tablets. J. Dev. Drugs. 2017;6(02):1-8.

12. Ramteke KH, Dighe PA, Kharat AR, Patil SV. Mathematical models of drug dissolution: a review. Sch. Acad. J. Pharm. 2014 Jan;3(5):388-96.

13. Costa P, Lobo JM. Modeling and comparison of dissolution profiles. European journal of pharmaceutical sciences. 2001 May 1;13(2):123-33.

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Review Article

Chemical Constituents, Cytotoxic Activities And Traditional Uses of *Murraya Koenigii* Linn :A Review

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ABSTRACT

For thousands of years, plants have been employed in traditional medicine. *Murraya koenigii*, a member of the Rutaceae family, is an aromatic leaf commonly used in Indian cooking. In traditional system of medicine, it is used as antiemetic, antidiarrhoeal, blood purifier, dysentery, febrifuge, tonic, stomachic, flavoring agent in curries and chutneys. The oil is used externally for bruises, eruption, in soap and perfume industry. The phytoconstituents isolated so far from the leaves are alkaloids, coumarin glycoside, essential oils, calcium, phosphorus, iron, thiamine, riboflavin, niacin, vitamin C, carotene and oxalic acid. It is reported to possess antioxidant, antibacterial, antifungal, larvicidal, anticarcinogenic, hypoglycemic, anti-lipid peroxidative, hypolipidemic and antihypertensive activities. Due to the presence of important phytochemicals, the plant possesses several pharmacological activities. This review compile the botanical description, traditional uses, chemical constituents and cytotoxic activities of different parts of Murraya koenigii.

Keywords: *Murraya koenigii*, alkaloids, traditional use, chemical constituents, cytotoxic activities.

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INTRODUCTION

Natural products provide unlimited opportunities for new drug discoveries due to incomparable availability of chemical diversity. It is estimated that 70-80% of people globally rely mostly on traditional, largely herbal, medicines to meet their primary healthcare necessities.[1] The demand for herbal medicine is not only large, but growing. Recently ricin, a toxin obtained from the beans of *Ricinus communis*, has been found to effectively couple to tumor targeted monoclonal antibodies and has proved to be a very potent antitumor drug.[2] HIV inhibitory activity has been found in some novel coumarins (complex angular pyranocoumarins) isolated from *Calophyllum lanigerum*.[3] Newly developed genetic engineering in plants has further increased their importance in the field of medicine, for example, in the production of

antibodies by expression of an appropriate gene in the plant.[4] Thus, by knowing the potential resources it is possible to increase the content of the important active compounds.

Murraya Koenigii, (L.) belongs to the family Rutaceae, usually known as curry-leaf tree is an aromatic leaf often used in Indian cuisine. [5] It is native to tropical Asia from Himalaya foothill's of India to Srilanka eastward through Myanmar, Indonesia, Southern China and Hainan.[6] It is a small tree, growing 4-6 m tall, with a trunk up to 40cm diameter. *M. koenigii* has grey color bark, longitudinal striatations on it and beneath it white bark is present. The leaves are highly aromatic and are bipinnately compound, 15-30 cm long each bearing 11-25 leaflets alternate on rachis, 2.5-3.5 cm long ovate lanceolate with an oblique base. Margins irregularly creatate, petioles 2-3 mm long, flowers are bisexual, white, funnel shaped sweetly scented, stalked, complete, ebracteate, regular with average diameter of fully opened flower being in average 1.12 cm inflorescence, terminal cymes each bearing 60-90 flowers. Fruits are ovoid to subglobose, wrinkled or rough with glands. It is having the size of 2.5 cm long and 0.3 cm in diameter and gets purplish black when ripen. Fruits are generally biseeded. Seeds generally occur in spinach green color, 11 mm long, 8 mm in diameter and weighs up to 445 mg [5.]

The leaves are extremely valued as seasoning, but in their fresh form, they have a short shelf life, and they don't keep well in the refrigerator They are also available dried, though the aroma is largely inferior. The leaves of *M. koenigii* are also used as a herb in Ayurvedic medicine.[5]

Chemical Constituents of *Murraya Koenigii* (L.) Chemical Constituents of *M. Koenigii* has been investigated for its bioactive compounds by many research groups. To date, various compounds were identified, ranging from alkaloids, carbohydrate, sterol, terpinene, isomahanimbine, terpenoids to flavonoids. Besides, many compounds have been identified from volatile and essential oil extracted from different parts of *M. Koenigii*. The significant chemical components [18] of different parts of *M. Koenigii* are listed in the table-1 below.

Table 1 :Chemical constituents found in different parts (Leaves, Seed, Stem bark, Root and fruit) of *Murraya koenigii* (L)

Plant Parts	Chemical constituents	Plant Parts	Chemical constituents
Leaves	Koenigine	Stem and bark	Mahanimbine
	Koenine,		Girinimbine
	Koenidine		Murrayanine
	(-) mahanine		Murrayazoline
	Mahanimbine		Murrayacine
	Isomahanimbine		Linalool
	Koenimbidine	Root	Bornyl Acetate
	Murrayacine		Bikoeniquinone
	Isomahanimbicine		Bicyclomahanimbine
	α -Copaene		Bis-3-Hydroxy-3- Methyl Carbazole
	α-Pinene		6,7-Dimethoxy 1-Hydroxy Carbazole
Seed	Terpinene		Girinimbilol
	Terpinen-4-ol, linolol		Iso Menthone
	Ocimene		Linalool
	Limblee		3-Methyl Carbazole
	Limbolee		Mahanimbine
	Simbolee		Mukoline
Stem and bark	Carbazole alkaloids		Murrayanol
	Coumarin galactoside,	Fruit	Girinimbine
	Carbazole carboxylic acid		Isomahanimbine (+)
	Glycolipids		Koenimbine
	Phospholipids		Terpinene

CYTOTOXIC ACTIVITIES

Although *M. koenigii* has been used for its therapeutic efficacy in different diseases, in this study we will investigate its cytotoxic activities which are summarized below:

HeLa cell line (cervical cancer cells)

- Amna *et al*, investigate the cytotoxic activity from three extracts of *Murraya koenigii* leaves against cervical cancer (HeLa) cell lines, including hexane, ethyl acetate, and methanol. In this study, the hexane extract containing some non-polar secondary compounds such as a group of terpenoids and steroids, some semi-polar chemical compounds such as alkaloids and flavonoids were present in the extract of ethyl acetate and the methanol extract contained polar chemical compounds such as tannins, saponins, and flavonoids. This study showed that all the three extracts

exhibited a potent cytotoxic activity for HeLa cancer cells in which hexane and ethyl acetate showed a very strong cytotoxic effect with a CD_{50} value of <1 µg/mL while methanol extract showed a cytotoxic effect with a CD_{50} value of 2.25 µg/mL.[8]

- The cytotoxic activity against cervical cancer (HeLa) cell lines was determined by the MTT colorimetric cell viability assay. This study showed that the hexane extract containing terpenoids isolated from the leaves of *M. koenigii* possesses strong cytotoxic activity against HeLa cell lines with CD_{50} values of <1 µg/mL.[7]

PC-3 cell line (human prostate cancer)

Kamalidehghan *et al* investigate that the effect of Koenimbin, a major biologically active component of the leaves of *M. koenigii* against the human prostate PC-3 cells and PC-3-derived prostate cancer stem cell (PCSCs). This study revealed that Koenimbin induces apoptosis in human androgen-independent PC-3 cells through the intrinsic or mitochondrial signaling pathway and suppression of translocation of cytoplasmic NF-κB into the nucleus.

In the study, the antiproliferative activity of koenimbin was examined by the MTT assay method and the apoptotic detection was performed using acridine orange/propidium iodide (AO/PI) double-staining and multiparametric high-content screening (HCS) assays. To validate the expression of apoptotic-associated proteins different methods such as Caspase bioluminescence assay, reverse transcription-polymerase chain reaction (RT-PCR), and immunoblotting were performed. In addition, some other methods such as cell analysis, the involvement of nuclear factor-kappa B (NF-κB), and examination of prostasphere formation were conducted.

It was found that Koenimbin induced nuclear condensation, the formation of apoptotic bodies, and the arrest of PC-3 cells in the G0 /G1 phase. Koenimbin also triggered the activation of caspase-3/7 and caspase-9 and the release of cytochrome c, decreased anti-apoptotic proteins such as Bcl-2 and HSP70, increased pro-apoptotic Bax proteins, and inhibited NF-κB translocation from the cytoplasm to the nucleus, resulting in the activation of the intrinsic apoptotic pathway. This study proposed that Koenimbin has chemotherapeutic potential that may be employed for future treatment .[9]

A549 cell lines (lung adenocarcinoma cells)

The cytotoxic activity of girinimbine, a carbazole alkaloid isolated from the roots of *Murraya koenigii* against A549 lung cancer cells was described by Mohan S and Co-workers. Girinimbine induces apoptosis of A549 cells by both intrinsic and extrinsic

pathways, which is dependent on caspase mediation. It mediates its antiproliferative and apoptotic effects through up- and downregulation of apoptotic and antiapoptotic proteins. In addition, this study also identified the downregulation of p53 as well as p27 and p21 repressor proteins for cell proliferation, and the main role of insulin / IGF-1 signaling.

In this study, the antiproliferative activity of girinimbine was assayed using the MTT assay method and it revealed that the girinimbine induces cell death with an IC_{50} of 19.01 μM. Such finding suggests that girinimbine could be a candidate for a novel anticancer agent.[10]

HT-29 cell line *(human colon cancer cell)*

Girinimbine, isolated from the leaves of *Murraya koenigii induce*s apoptosis in human colon cancer *HT-29* cell lines. In this study, cell viability and proliferation were performed by the MTT assay method. It showed that girinimbine possesses significant cytotoxic activity against the HT-29 cell lines at 24 hours in a dose-dependent manner with an IC_{50} of 4.79±0.74 µg/mL. This investigation suggests that, for the potential use of girinimbine as an anticancer agent, further improvement of its current structure may also be considered.[11]

MCF-7 cell line (human breast cancer cells)

The anticancer effect of koenimbin, isolated from the leaves of *Murraya koenigii* inhibit the MCF7 breast cancer cells and target MCF7 breast cancer stem cells through apoptosis was described by Ahmadipour and colleagues. This study evaluated the effect of koenimbin on MCF7 cells using MTT assays in a dose-dependent manner. After 24, 48, and 72 hours of treatment of MCF7 cells with koenimbin, the obtained IC_{50} values were 9.42±1.05 µg/mL, 7.26±0.38 µg/mL, and 4.89±0.47 µg/mL, respectively.[12]

AMC-HN-8 cell line (human laryngeal cancer cells)

Li L. and Collogues evaluated the cytotoxic effects of Mukonal, a carbazole alkaloid isolated from the *Murraya koenigii* on the AMC-HN-8 laryngeal cancer cell line. In the study, the result shows that due to the induction of apoptosis and G2/M cell cycle arrest, mukonal reduced the viability of the AMC-HN-8 cells in a dose-dependent manner with an IC_{50} value of 10 µM.[13]

Plant extracts or constituent's	**Intensity of cytotoxicity**
Hexane extract of leaves	Showed strong cytotoxic activity against cervical cancer (HeLa) cell lines with a CD_{50} value of <1 µg/mL.

Ethyl acetate extract of leaves	Showed strong cytotoxic activity against cervical cancer (HeLa) cell lines with a CD_{50} value of <1 µg/mL.
Methanol extract of leaves	Showed strong cytotoxic activity against cervical cancer (HeLa) cell lines with a CD_{50} value of 2.25 µg/mL
Girinimbine	Possesses significant cytotoxic activity against lung adenocarcinoma (A549) cell lines with IC_{50} value of 19.01 μM. Possesses strong cytotoxic activity against HT-*29 cell line* (human colon cancer cell) with an IC_{50} of 4.79±0.74 µg/mL.
Koenimbin	Exhibit significant cytotoxic activity against with MCF-**7 cell line (human breast cancer cells) with** IC_{50} values were 9.42±1.05 µg/mL, 7.26±0.38 µg/mL, and 4.89±0.47 µg/mL, respectively.
Mukonal	Possesses moderate cytotoxic activity against the AMC-HN-8 cell line (human laryngeal cancer cells) with a IC_{50} value of 10 µM.

TRADITIONAL USES

Murraya koenigii, also called curry leaf plant, is well known for its aromatic nature and medicinal properties.[14] Traditionally, powder of fresh leaves and essential oils of *M. koenigii* are used as flavoring agents in various food items.[15] The roots and bark are applied to the skin in case of bites of poisonous animal and skin rash. The fruit of *M. koenigii* is used as an astringent in the Indochina region.[16] Fresh juice from green curry leaves combined with sugar and lime has been used for the treatment of morning sickness, vomiting, and indigestion. Curry leaf paste is consumed with buttermilk to treat stomach upset.[17] In whole or in parts, curry leaves are used as anti-fungal, anti-rheumatic, anti-inflammatory, blood purifying agents in traditional practice. Fresh *Murraya koenigii* leaves are used as a hair tonic to maintain the normal black hair color and hair growth.[15]

CONCLUSION

In current years, ethnobotanical and traditional uses of natural compounds, especially from plant sources received great attention as they are well tested for their efficacy and generally believed to be safe for human use. *Murraya Koenigii* has a wide range of medicinal properties. For drug discovery more specifically for anticancer drugs, this plant may be considered as a potential candidate. This review compiled cytotoxic properties, traditional uses and chemical constituents of the plant which will help a researcher to develop and design a drug based on cytotoxic properties and also

facilitate researchers who are finding a source for a particular compound.

REFERENCES

1. Brahmi F, Achat S, Guendouze-Bouchefa N, Benazzouz-Smail L, Elsebai MF, Madani K. Recent advances in the identification and the study of composition and activities of medicinal plants. *J Coast Life* Med. 2016;4(12):983-99.
2. Halling KC, Halling AC, Murray EE, Ladin BF, Houston LL, Weaver RF. Genomic cloning and characterization of a ricin gene from Ricinus communis. Nucleic Acids Res. 1985 Nov 25;13(22):8019-33.
3. Kostova I. Coumarins as inhibitors of HIV reverse transcriptase. Curr. HIV Res. 2006 Jul 1;4(3):347-63.
4. Słomińska-Wojewódzka M, Sandvig K. Ricin and ricin-containing immunotoxins: insights into intracellular transport and mechanism of action in vitro. Antibodies. 2013 Jun;2(2):236-69.
5. Hema R, Kumaravel S, Alagusundaram K. GC/MS determination of bioactive components of Murraya koenigii. Journal of American Science. 2011;7(1):80-3.
6. Handral HK, Pandith A, Shruthi SD. A review on Murraya koenigii: multipotential medicinal plant. Asian J Pharm Clin Res. 2012;5(4):5-14.
7. Amna U, Halimatussakdiah PW, Saidi N, Nasution R. Evaluation of cytotoxic activity from Temurui (Murraya koenigii [Linn.] Spreng) leaf extracts against HeLa cell line using MTT assay. J. Adv. Pharm. Technol. Res. 2019 Apr;10(2):51.
8. Amna U, Halimatussakdiah H, Wahyuningsih P, Saidi N, Nasution R, Astryna SY. Phytochemical screening and In vitro Cytotoxic activity of Hexane extract of Temurui (Murraya koenigii (Linn.) Spreng) leaves against Human Cervical Cancer (HeLa) cell line. IOP Conf. Ser.: Mater. Sci. Eng. 2019 May;523(1):012018. Available from: https://iopscience.iop.org/article/10.1088/1757-899X/523/1/012018 DOI:10.1088/1757-899X/523/1/012018
9. Kamalidehghan B, Ghafouri-Fard S, Motevaseli E, Ahmadipour F. Inhibition of human prostate cancer (PC-3) cells and targeting of PC-3-derived prostate cancer stem cells with koenimbin, a natural dietary compound from Murraya koenigii (L) Spreng. Drug Des Devel Ther. 2018 May; 12:1119-33. Available from:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5942175/
DOI: 10.2147/DDDT.S156826

10. Mohan S, Abdelwahab SI, Cheah SC, Sukari MA, Syam S, Shamsuddin N, et al. Apoptosis effect of girinimbine isolated from Murraya koenigii on lung cancer cells in vitro. Evid Based Complement Alternat Med. 2013 Jan;2013. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3610346/ DOI: 10.1155/2013/689865
11. Iman V, Mohan S, Abdelwahab SI, Karimian H, Nordin N, Fadaeinasab M, et al. Anticancer and anti-inflammatory activities of girinimbine isolated from Murraya koenigii. Drug Des Devel Ther. 2017;11:103-121. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5207336/ DOI: 10.2147/DDDT.S115135
12. Ahmadipour F, Noordin MI, Syam Mohan AA, Paydar M, Looi CY, Keong YS, et al. Koenimbin, a natural dietary compound of Murraya koenigii (L) Spreng: inhibition of MCF7 breast cancer cells and targeting of derived MCF7 breast cancer stem cells (CD44+/CD24−/low): an in vitro study. Drug Des Devel Ther. 2015 Feb;9:1193-208. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4346015/ DOI: 10.2147/DDDT.S72127
13. Li L, Huizhi L, Binu W, Xinxin D, Longjun W, Liping Y, et al. Anticancer activity of mukonal against human laryngeal cancer cells involves apoptosis, cell cycle arrest, and inhibition of PI3K/AKT and MEK/ERK signalling pathways. Med. Sci. Monit. 2018 Oct;24:7295-302. Available form: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6195788/ DOI: 10.12659/MSM.910702
14. Dutt R, Dalal J, Singh G, Gahalot SC, Chandolia RK. Medicinal Uses of Murraya koenigii and Aegle marmelos for Fertility Augmentation in Animals: A Review. Int J Curr Microbiol Appl Sci. 2018 Sep;7(9):645-57.
15. Balakrishnan R, Vijayraja D, Jo SH, Ganesan P, Su-Kim I, Choi DK. Medicinal profile, phytochemistry, and pharmacological activities of Murraya koenigii and its primary bioactive compounds. Antioxidants. 2020 Feb;9(2):101. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7070712/ DOI: 10.3390/antiox9020101
16. Muthumani P, Venkatraman S, Ramseshu K, Meera R, Devi P, Kameswari B, et al. Pharmacological studies of anticancer, anti-inflammatory activities of Murraya koenigii (Linn) Spreng in experimental animals. J. Pharm. Sci. & Res. 2009;1(3):137-141.

17. Nishan M, Subramanian P. Murraya koenigii (curry leave)-A review on its potential. Int. J. Pharmtech Res. 2015;7(4):566-72.
18. Handral HK, Pandith A, Shruthi SD. A review on Murraya koenigii: multipotential medicinal plant. Asian Journal of pharmaceutical and clinical research. 2012;5(4):5-14.

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Research Article

Disposal Practice of Unused Medicine in Dhaka, Bangladesh: A Cross-Sectional Study

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ABSTRACT

There is a greater understanding that incorrect disposal of unused drugs can harm the environment. The study aimed to identify the percentage of unused drugs and how they were disposed of in Dhaka, Bangladesh. An in-depth interview based qualitative study, consisted of a series of questions with predefined answer sets and queries about the collection of medications, reasons for unused, storage of drugs and their disposal methods. A total of 200 people took part in this survey and unwanted drugs were found in the homes of the 58% respondents. The most prevalent cause for having residual medication was that the patient's medical condition had alleviated or healed (40%). Depending on the type of formulation, between 16–23% of unused medicines were returned to medicine shops; capsules and tablets returned mostly but liquids were put to sewage systems. According to the findings of this study, a considerable percentage of unused medications are disposed of through drainage systems that have the potential to harm the environment. Excess drugs and wastage can be reduced, and proper disposal practices can be taught to reduce their environmental impact.

Keywords: Unused drugs; Disposal method; Pharmacy; Bangladesh.

INTRODUCTION

Unused medication, often known as unused prescriptions, might suggest either over-prescribing by doctors or poor drug adherence on the part of patients. Unused medication wastes resources, increases pathogen resistance, and leads in sub-optimal chronic disease management. Pharmaceutical waste products have been found in the environment, where they have been proved to have a negative impact in some circumstances.[1] These wastes are produced when unused medications are disposed of in an environmentally undesirable manner, such as in the sink, toilet, or garbage can. Solid tablets and capsules were more likely to be thrown away than liquid drugs, which were more likely to be washed away in the sink. In many countries, returning leftover drugs to

community pharmacies is one of the suggested options for households to dispose of them. The worldwide rising use of pharmaceuticals has elevated international awareness of the potential environmental harm that these compounds might create when disposed of in landfills or in waterways.[2]. Even small amount of ethinyl estradiol (the active ingredient in a common oral contraceptive) found in waterways, for example, have been proven to affect sexual development and increase fish feminization.[3] There's also evidence that antibiotics in water have an effect on the bacteria that live there, possibly leading to antibiotic resistance.[4] Medication that has been improperly disposed of could constitute a severe environmental concern[5] and storing of unused pharmaceuticals in the home increases the danger of accidental poisoning in children.[6,7] Pharmaceuticals can have negative consequences on wildlife in some cases. The non-steroidal anti-inflammatory medicine (NSAID) diclofenac, for example, has been proven to cause renal failure in vultures after they ate carrion from cattle treated with the drug.[7] Pharmaceutical residues have been found in effluents from sewage facilities, surface water, and drinking water on a regular basis. The issue of unused pharmaceuticals at home has never been investigated in Bangladesh. To evaluate the possible environmental effects of improperly discarded medicine in Bangladesh, researchers must first figure out how many unused drugs are currently not returned to pharmacies and are just disposed of in landfills or water mains.

METHODS AND MATERIALS An in-depth qualitative interview research was undertaken from May, 2014 to August, 2014.A total of 200 patients from different areas in Dhaka, Bangladesh were participated in this study.

Sampling Procedure and Frame

Individuals who spoke Bengali and lived in Bangladesh and were at least 20 years old were the target group. In each step, the ‘samples' were chosen at random and were nationwide and representative of the entire country. The sample procedure consisted of two steps: first, a household was randomly selected, and then a household member was randomly selected. If the appropriate person was unavailable, he or she was replaced by a randomly picked household member or a randomly selected household. Following the identification of the participants, an appointment was set to conduct the interview at their homes.

Questionnaire Development and Contents

The goal of this study was explained to the participants before they were interviewed, and their verbal consent was obtained. The interviewer distributed the questionnaire to each individual respondent and collected the question-sheet with their responses. There were two sections in the questionnaire. The first section requested demographic information such as age, sexuality, ethnicity, educational qualification, earnings, drug costs, medication types utilized, and so on. A combination of questions with predefined answer sets were utilized in the second segment to inquire about medication collection, why there may be unneeded medications, how they are preserved, and how they are disposed of.

Data analysis

The SPSS software (Version 21.0; SPSS, Inc, Chicago, IL) was used to enter and analyze all of the data. The results of a descriptive data analysis were given as frequencies and percentages.

RESULTS AND DISCUSSION

A medicine disposal take-back program is an useful way to get rid of expired, unwanted, or unused medicines from people's homes and lessen the risk of others mistakenly taking the medicine. As a result, we must take a few basic measures to properly and responsibly dispose of our old and unused prescriptions. Find out if there are any particular requirements about which drugs can be returned for safe disposal if our community has a medicine take-back program.

A total of 200 participants were approached regarding their unused drug disposal methods and out of 200 participants, 58% (n=116) respond at all to the survey objectives, thus 116 were considered as sample (Table 1).

Table 1. Characteristics of study population (N=116)

Item	N (%)
Survey faced	200 (100%)
Did not meet the criteria	84 (42%)
Considered as sample	116 (58%)
Collect all the medicines at a time	60 (51%)
Collect the medicines on refill basis	22 (19%)

Regardless of whether they thought they would need them or not, 51% of respondents got all of their doctor's prescriptions from a pharmacy. Even if the patient believes the prescriptions are not needed or wanted, 19% claimed they collect all of their monthly pharmaceutical refills. (Table 1). Respondents' most common explanation for having leftover medications was that their medical condition had improved or resolved (40%). Other reasons included: 'changed to another treatment' (14%), 'excess quantity supplied' (12%), 'expiration date passed' (11%), 'side-effects of medication' (10%), 'unsure why medication was prescribed' (6%), 'inconvenience to follow instructions' (4%), 'medicine labels had uncertain instructions' (2%), and 'patient deceased' (1%) (Table 2).

Table 2. Reasons behind leftover medicines (N=116)

Item	N (%)
Improved medical conditions or resolved	47 (40%)
Changed to other treatments	16 (14%)
excess quantity supplied	14 (12%)
Passed expiry dates	13 (11%)
Side effect of medicines	12 (10%)
Unsure about prescribed medicines	7 (6%)
Inconvenience or difficulty following instructions	5 (4%)
Medicine labels had unclear instructions	3 (2%)
Patient deceased	2 (1%)

Unused medications that are not returned to the pharmacies are more likely to be found in a landfill as solid waste or thrown down the toilet as an element of liquid drainage.

According to a research conducted by Statistics Canada[8], around a quarter of Canadian families produce leftover drugs. A considerable majority of the homes with unwanted prescriptions continued to dispose of them through the sewer, garbage, or burial, ranging from 20 to 70 %. According to a research conducted in Kuwait, three-quarters of respondents said they threw away undesired drugs in the garbage.[9] In a study conducted in the United States, 54% respondents said they threw away undesired drugs in the trash, while 35% said they flushed them down the toilet or poured them down the drain.[10] In a 2005 poll in the United Kingdom, 63 percent of respondents said they threw away unwanted prescriptions in the trash, 11% said they poured them into the sink or toilet, and 22% said they returned them to a pharmacy.[11] According to a recent survey from New Zealand, between 13% and 24% of drugs were returned to a pharmacy.[12] In a recent Swedish investigation, the researchers discovered that none of the volunteers flushed the medications down the toilet.[13] This could be because in Sweden, pharmacists provide special clear plastic bags with explanatory wording in which unused drugs should be deposited. A Canadian survey found that 46% of respondents flushed undesired medication down the drain.[14]

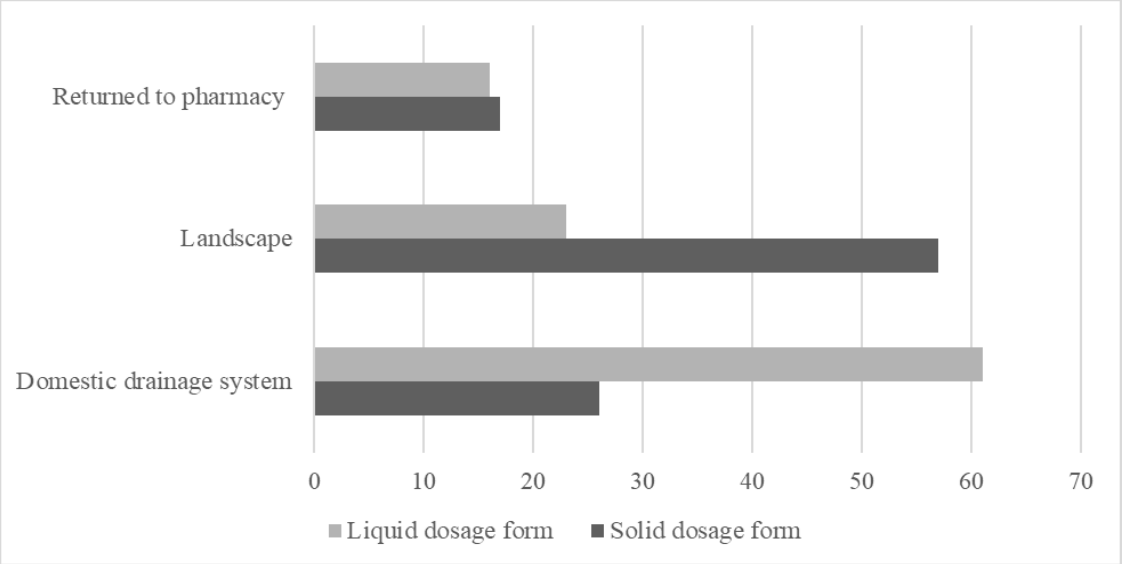

Figure 1. Fate of leftover medicines (N=116)

In our survey, 61% of respondents said they throw away undesired liquid medicines down the toilet or into the sink. Another 23% dispose of liquid pharmaceuticals in a waste disposal system that eventually ends up in a landfill. Only 16% of people take these prescriptions back to the pharmacy to be disposed of. When it comes to solid dosage forms (tablets and capsules), more individuals reported disposing of them in a landfill (57%) than in the water system (26%), with only 17% returning unwanted medications to a pharmacy. In our current survey, the majority of participants (85%) stated that schools, universities, and public campaigns were the best ways to educate the public about unwanted drug disposal. The findings of this study imply that patient education on how to properly dispose of unused and expired drugs could be beneficial. Patient education may be a factor, since frequent visits to the pharmacy were linked to previous returns to a pharmacy, and now being on more prescriptions was linked to previous returns to a provider. Although the current study indicates that a good

proportion of unwanted prescribed medicines material is disposed away in landfills or added into sewage systems in Dhaka, Bangladesh, few measurements of these compounds in the Bangladesh environment, either in parent form or in a degraded form resulting from chemical degradation, appear to have been reported. Current research, however, clearly shows that even low quantities of several of these substances can have a negative impact on the environment by interfering with biological activity. As a result, it is important that all elements of pharmaceutical usage and disposal be examined thoroughly in Bangladesh.

CONCLUSION

Pharmaceutical waste from clinics, hospitals, residences, and health systems is commonly disposed of in landfills or poured into a sink or toilet, where it eventually ends up in the sewer system. If these drugs are not biodegraded or eliminated during sewage treatment, they will eventually end up in drinking water. In fact, most sewage and water treatment plants ignore pharmaceutical contaminants, allowing them to enter our surface, ground, and drinking water untreated. The goal of this study was to determine how to dispose of unused and unwanted medication in Dhaka, Bangladesh. According to the findings of this study, dispensing policies that deduct the volume of medication are needed.

CONFLICT OF INTERESTS: The authors declare 'No conflict of Interest.'

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REFERENCES

1. Strand LM, Morley PC, Cipolle RJ, Ramsey R, Lamsam GD. Drug-related problems: their structure and function. Decp, 1990; 24 (11): 1093-7.
2. Halling-Sørensen BN, Nielsen SN, Lanzky PF, Ingerslev F, Lützhøft HH, Jørgensen SE. Occurrence, fate and effects of pharmaceutical substances in the environment-A review. Chemosphere, 1998;36(2):357-93.
3. Jobling S, Williams R, Johnson A, Taylor A, Gross-Sorokin M, Nolan M, Tyler CR, van Aerle R, Santos E, Brighty G. Predicted exposures to steroid estrogens in UK rivers correlate with widespread sexual disruption in wild fish populations. Environmental health perspectives, 2006;114(Suppl 1):32-9.
4. Costanzo SD, Murby J, Bates J. Ecosystem response to antibiotics entering the aquatic environment. Mar pollut bullet, 2005;51(1-4):218-23.
5. Daughton CG. Cradle-to-cradle stewardship of drugs for minimizing their environmental disposition while promoting human health. I. Rationale for and avenues toward a green pharmacy. Environmental Health Perspectives. 2003;111(5):757-74.
6. Beirens TM, Van Beeck EF, Dekker R, Brug J, Raat H. Unsafe storage of poisons in homes with toddlers. Accid Anal Prev. 2006;38(4):772-6..

7. Franklin RL, Rodgers GB. Unintentional child poisonings treated in United States hospital emergency departments: national estimates of incident cases, population-based poisoning rates, and product involvement. Pediatrics. 2008;122(6):1244-51.
8. Statistics Canada. Disposal of household special wastes (2005). Available from: http://www.statcan.ca/english/freepub/16-002-XIE/2008001/10539-en.htm.
9. Koshy S. Disposal of unwanted medications: throw, bury, burn or just ignore?. International Journal of Pharmacy Practice. 2013;21(2):131-4.
10. Kuspis DA, Krenzelok EP. What happens to expired medications? A survey of community medication disposal. Vet Hum Toxicol. 1996;38(1):48-9.
11. Bound JP, Voulvoulis N. Household disposal of pharmaceuticals as a pathway for aquatic contamination in the United Kingdom. Environ Health Perspect, 2005;113(12):1705-11.
12. Braund R, Peake BM, Shieffelbien L. Disposal practices for unused medications in New Zealand. Environ Int. 2009;35(6):952-5
13. Persson M, Sabelström E, Gunnarsson B. Handling of unused prescription drugs—knowledge, behaviour and attitude among Swedish people. Environ Int. 2009;35(5):771-4.
14. Boivin M. The cost of medication waste. Can Pharmaceut J. 1997;130(4):32-40.

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Review Article

A Review on Development of Anticancer Drugs from Natural Sources

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ABSTRACT

Disease is one of the main sources of death and there is a continuous increment in the number of malignancy cases around the world. New treatments to treat and forestall this perilous infection are continually being requested. Plants have been used for therapeutic purposes since pre-historic times and constitute the foundation of modern medicine. Indisputably, plants have emerged as important sources of therapeutics for the treatment of human cancers; notable ones include paclitaxel, vincristine, and vinblastine. In contrast to conventional medications, like chemotherapy, logical and research interest draws attention to mixtures made from natural compounds since they are thought to have less poisonous effects. The majority of today's cancer treatment research is focused on common products derived from plants. This article presents a review on anticancer items and their analogs, as well as novel plant species having anticancer properties *in-vivo* or *in-vitro*.

Keywords: Anticancer, Treatment, Drug, Medicinal plant, Natural compounds

INTRODUCTION

Cancer is a term used to describe a group of diseases in which some of the body's cells begin to proliferate uncontrollably and spread into adjacent tissues. Cancer is caused by alteration of genes that can be inherited or caused by exposure to chemicals, & radiation such as ultraviolet rays[1]. There are several varieties of cancer, which are typically called after the organs or tissues where they develop i.e. Lymphoma cancer begins in lymphocytes[2]. Some cancer patients undergo only one treatment, but the vast majority receive a combination of therapies, including surgery, chemotherapy, and/or radiation therapy. Cancerous cells are not killed immediately by radiation treatment. It might take days or weeks for cancer cells to die due to DNA damage[3]. On the contrary, chemotherapy destroys cancer cells but also

kills healthy cells that produce side effects include mouth sores, nausea, and hair loss[4]. Furthermore, immunotherapy and hormonal therapy are also used in cancer treatment as adjuvant therapy that reduces the possibility of cancer recurrence after primary therapy[5].

Since ancient times, plants use all cultures as well as the source of medicines for health benefits. Traditional medicines are used by around 80-85% of the world's population for their primary healthcare needs, and plant extracts or active principles are considered to be employed widely in traditional therapy. The main drawbacks of synthetic drugs are the side effects associated with them alternatively, natural treatments, such as the usage of plants or plant-derived natural compounds, be effective in the fight against cancer. The search for anti-cancer drugs from plant sources began in the 1950s when the vinca alkaloids (vinblastine & vincristine) were discovered and developed, as well as the isolation of cytotoxic podophyllotoxins. Approximately five decades of systemic drug discovery and development have resulted in the development of systematic tools and methods for finding chemotherapeutic drugs, as well as several significant advances in cancer therapy and care. However, more effective and selective anticancer drugs have yet to be discovered; also, these medicines have little effect on survival rates. Medical oncologists, scientists, and researchers from all around the world have contributed to solve this challenge.

High-throughput chemistry (i.e., combinatorial chemistry technique) and high-throughput screening are now the most prominent strategies since they allow for the fast development and assessment of huge numbers of candidate compounds. Entire libraries of potentially bioactive synthetic peptides, oligonucleotides, and tiny chemical compounds have been synthesized and tested in this manner. However, because of the weak pharmacological properties of peptides and oligonucleotides, as well as the lack of chemical variety of "drug-like" tiny organic molecules, the findings produced so far have fallen short of expectations. These limitations lead to the re-evaluation of other major sources of chemical diversity that has consistently proven their value for the development of novel drugs, which are natural products[6].

With the positive reception of the significance of natural products as sources for structurally novel and mechanistically unique drugs and the enormous biodiversity of Bangladesh, we were privileged to collect information by literature review and generate a database of medicinal plants, extracts, and isolated compounds having anticancer properties in this study, which will facilitate us for further exploration anticancer drugs in terms of synthetic chemistry approach.

MATERIALS AND METHODS

All articles having the terms anticancer, treatment, drug, medicinal plant, natural compounds in the abstract were searched on PubMed, Google Scholar, Biomed Central, World Health Organization, and National Cancer Institute. To avoid redundancy of information and to select more current evidence, the search was then limited to articles published within the last two decades. All of the abstracts were reviewed independently, and relevant articles were picked based on an agreement among the authors. Based on their relevance to the subtopics, 37 articles were screened for final analysis.

RESULT

Anticancer activity of natural products

The study describes the plant-derived compounds, their occurrence, and varieties of action mechanisms, such as microtubular binding, topoisomerase inhibition, DNA binding, cell cycle arrest, and apoptosis. Their properties have been tested on various cancer cell lines, experimental animals, and human chemotherapy. The work presents existing anticancer drugs that have been approved for usage, as well as newer analogies and other less known anticancer agents that might be used in cancer treatments. Natural compounds from plants and the marine environment are presented in terms of their uses, mechanisms of action, and doses[7-9].

Table 1. List of natural compounds having anticancer property

Identified compounds	Source	Studied cell line/s	Proposed mechanism
Catharanthus alkaloids	*Catharanthus roseus*	Acute Lymphocytic Leukemia, Lung Cancer, Bladder Cancer	Inhibit mitosis and cause apoptosis.
Viscum Album extract	*Viscum album*	Human Colon Cancer Cells (Colo 320 HSR) Breast Cancer Cells (MFM-223, HCC–1937, KPL-1, MCF-7)	Activation of apoptosis and early cell cycle inhibition.
Taxanes	*Taxusbaccata, Taxusbrevifoli*	Breast Cancer Cells (MCF-7), Cervical Carcinoma (Hela), Adenocarcinoma (HT29, OVG-1, PC-Sh, A549), Human Lung Cancer (A549)	Mitosis inhibition by affecting the microtubules.
Combretastatin	*Combretum caffrum*	Human Thyroid Papillary Carcinoma Cell (TPC1)	Destabilization of the microtubules.
Geniposide	*Gardenia jasminoides*	Human Lung Cancer Cell (H1299)	Initiation of the mitochondrial death cascade.
Colchicine	*Colchicum genus*	Hepatocellular Carcinoma Hepg2	Limit mitochondrial metabolism in the cancer cell.
Artesunate	*Artemisia annua*	Chronic Myeloid Leukemia (K562)	Antiangiogenic effect inhibits VEGF expression.

Elipticine	*Ochrosia elliptica Labill*	Leukemia (HL-60, CCRF-CEM) cells	Disrupts the cell cycle by regulating the expression of some kinases.
Roscovitine	*Raphanus sativus L.-Brassicaceae*	Highly metastatic & invasive breast cancer cells MDA-MB231	Inhibits cyclin-dependent kinase (CDK) activity leading to cell-cycle arrest in the G1 & G2 phases.
Maytansin	*Maytenusserrata L-Celastraceae*	COLO 205 cells	Inhibits microtubule assembly by binding to tubulin.
Bruceantinn	*Bruceaantidys enterica*	Human pancreatic cancer cells (PANC-1, SW1990)	Inhibits protein synthesis by inhibiting peptidyl transferase.

Review on *in-vivo* and/or *in-vitro* studies on plants with anticancer activity

Achyranthes aspera

The methanol extract of *Achyranthes aspera*, its alkaloid, non-alkaloid, and saponin fractions showed significant anticancer properties on carcinogen in Raji cells (at a concentration of 100µg). The total methanol extract had a pronounced cytotoxic activity *in-vivo* two-stage skin carcinogenesis test[10].

Allium Sativum

In male Wistar rats, administration of *Allium sativum* (garlic) (250 mg/kg, p.o., three times a week) substantially reduced 4-nitroquinoline-1-oxide-induced tongue carcinogenesis, as shown by the carcinomas[11].

Andrographis paniculata

Ethanol extract of *Andographis paniculata* contains 14 compounds with cytotoxic activities; a majority of them are flavonoids and labdane diterpenoids. Its methanol extract was separated, and the dichloromethane fraction was found to have three active components that were tested and shown to have cytotoxic and immunostimulatory properties[12].

Annona muricata

Annona muricata acetogenins have been found to be toxic to a variety of cancer cell lines such as human breast cancer, tumor carcinoma, pancreatic carcinoma, prostatic & colonic adenocarcinoma, human lymphoma, liver cancer, and multidrug-resistant adenocarcinoma of the human breast[12-13].

Bidens pilosa

Bidens pilosa extracts of hexane, chloroform, and methanol and their fractions were tested on different lines of cancer cells and showed remarkable antitumor activity[13].

Bolbostemma paniculatum

Tubeimosides obtained from *Bolbostemma paniculatum* by extraction and further fractionation showed promised cytotoxic activity that may be associated with DNA synthesis inhibition and may induce phenotypic reverse tumor cell transformation[14].

Centaurea ainetensis

The crude extract of *Centaurea ainetensis* suppressed the proliferation of a variety of cancer cells isolated from the colon. Salograviolide-A obtained by further

fractionation reduced the growth of colon cancer cell lines at non-cytotoxic levels besides exhibiting potent cytotoxic action against epidermal squamous cell carcinogenesis[13, 15].

***Camellia sinensis* (Green Tea)**

Epigallocatechin-3-gallate (EGCG), the most abundant polyphenol in green tea, inhibited human colon and oral cancer cells. Furthermore, it also inhibits the growth of cancer cell lines such as hepatocellular and ovarian carcinoma (HEY & OVCA)[12, 16].

Daphne mezereum

Hydro-alcohol extract of *Daphne mezereum* has had a powerful antileukemic activity in mice against lymphocytic leukemia. Mezerein was isolated and identified as a potent antileukemic molecule upon further fractionation studies on the extract[9, 16].

Hydrocotyle asiatica

Hydrocotyle asiatica leaf aqueous extract exhibited remarkable cytotoxicity against mouse melanoma, human breast cancer, and rat glioma cell lines. It's cytotoxic and antitumor effects have a direct impact on DNA synthesis[16].

Hypericum Perforatum

Hypericin, the active constituent isolated from *Hypericum perforatum*, inhibited protein kinase-C, which was measured by thymidin intake, and lowered and retarded the growth of glioma cell lines in vitro, as well as causing glioma cell death. Hypericin's ability to suppress glioma cells was comparable to or greater than that of the standard reference drug tamoxifen. The inhibitory action of *Hypericum perforatum* was related to its components, which block serotonin reuptake and hence suppress cell development in various cancer cell lines in vitro and *in-vivo*[12].

Oroxylum indicum

In selected cell lines tested, extensive cytotoxicity has been shown for the methanolic and aqueous extracts of *Oroxylum indicum*, with the methanolic extract showing higher cytotoxic potential. Both extracts showed moderate protective levels of DNA against oxidative stress[13, 15].

Rubia cordifolia

Mollugin, a cytotoxic compound obtained from *Rubia cordifolia*, showed significant activity against lymphoid leukemia in mice, as well as passive cutaneous anaphylaxis suppression and mast cell degranulation protection in rats[12, 16].

Salvia miltiorrhiza

Tanshinone-I and II, which were extracted from *Salvia miltiorrhizae*, had an anticancer effect on breast cancer cells and caused them to kill via apoptosis[13, 15].

Silybum marianum

Flavonoid compounds (Silymarin & Silibinina) obtained from *Silybum marianum* have been found to regulate gene products involved in human breast cancer proliferation, invasion, angiogenesis, and metastasis[9, 16].

Smilax china

The active constituent of *Smilax china* is Kaempferol-7-O-beta-D-glucoside, a flavonoid glycoside that exerted a significant anticancer effect on human cervix carcinoma cells by stopping the cell cycle and inducing apoptosis[13, 15].

Strychnos nuxvomica

Major constituents of *Strychnos nuxvomica* are alkaloidal and effective against HepG2 cell growth, with brucine alkaloid causing HepG2 cell death by apoptosis, including caspase-3 and cyclooxygenase-2[12].

Taraxacum officinale

Taraxacum officinale leaves, flowers, and root extracts were investigated against processes related to tumor progressions such as invasion and proliferation. It significantly increased the production of tumor necrosis

factor and interleukin (IL)-1α, thereby inhibiting the proliferation of breast cancer cells[15].

Withania somnifera

The growth of cancer cells in human breast, central nervous system, lung, and colon cancer lines comparable to doxorubicin, which was used as a standard drug, was reduced by an *in-vitro* study of withanolides from *Withania somnifera*[13, 15].

Zingiber officinale

The ethanol extract of *Zingiber officinale* reduced the risk of skin tumor and colon cancer incidence in mice. The suggested mechanism of action on colon cancer cells can be its suppression and arrest of the G0/G1 phase, reduction of DNA synthesis, and apoptosis[12, 16].

DISCUSSION

Natural compounds have assumed greater importance in new drug development, particularly for cancer and infectious diseases[17]. Natural products have distinct properties that offer both benefits and challenges for drug development when compared to traditional synthetic molecules. Natural compounds may undergo chemical modification before they may be established into effective drugs. Moreover, taking a molecule into clinical development necessitates a long-term, cost-effective source of adequate amounts of the compound. Researchers are continually improving and optimizing existing ones, utilizing innovations in biosynthetic engineering, and semi-synthetic approaches, aside from looking for novel natural compounds with anticancer properties. The ability of certain Phytochemicals to specifically stimulate the host immune response against cancer cells might increase response rates to immune checkpoint inhibitors by transforming 'cold' tumors 'hot,' is a significant prospect in this research[18].

New advancements in chemical synthesis and biosynthetic engineering technologies have greatly facilitated natural compounds-based drug discovery and development by allowing property optimization of previously inaccessible complicated compound scaffolds. As summary we concluded that natural compounds remain a prospective source of bioactivities that can be developed directly or utilized as a foundation for the development of new anticancer drugs.

CONCLUSION

This review concludes that herbal medicinal plants and their constituents are effective against different type of cancers such as lymphoma, breast cancer, ovarian cancer, lung cancer, liver cancer, prostate cancer, and testicular cancer. It is an excellent option for rural and underprivileged individuals who want to treat cancers of several types with low-cost natural drugs. Many compounds obtained from plants and aquatics are used in modern chemotherapy, which has cytotoxic effects and a variety of action mechanisms. Therapeutic strategies based on drugs will currently predominate in the 21st century. Therefore, finding novel drugs that are effective against resistant cancers is an important and necessary strategy for improving chemotherapy. Natural drugs, such as paclitaxel, vincristine, and camptothecin, have direct medical use as therapeutic entities, but they also serve as chemical models or templates for the design, synthesis, and semi synthesis of novel drugs in the treatment of human cancer. Although there are some new drug discovery approaches, such as combinatorial chemistry and computer-based molecular modeling design, none of them can take the position of natural products in drug discovery and development.

REFERENCES

1. Jackson M, Marks L, May GH, Wilson JB. The genetic basis of disease. Essays in biochemistry. 2018 Dec 3;62(5):643-723.
2. Philpott D. Critical government documents on law and order. Bernan Press; 2016 Jul 26.
3. Baskar R, Lee KA, Yeo R, Yeoh KW. Cancer and radiation therapy: current advances and future directions. International journal of medical sciences. 2012;9(3):193.
4. Chabner BA, Roberts TG. Chemotherapy and the war on cancer. Nature Reviews Cancer. 2005 Jan;5(1):65-72.
5. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, Stein KD, Alteri R, Jemal A. Cancer treatment and survivorship statistics, 2016. CA: a cancer journal for clinicians. 2016 Jul;66(4):271-89.
6. Mans DR, Da Rocha AB, Schwartsmann G. Anti-cancer drug discovery and development in Brazil: targeted plant collection as a rational strategy to acquire candidate anti-cancer compounds. The oncologist. 2000 Jun;5(3):185-98.
7. Cragg GM, Newman DJ. Plants as a source of anti-cancer agents. Journal of ethnopharmacology. 2005 Aug 22;100(1-2):72-9.
8. Tomlinson TR, Akerele O, editors. Medicinal plants: their role in health and biodiversity. University of Pennsylvania press; 2015 Jun 30.
9. Lichota A, Gwozdzinski K. Anticancer activity of natural compounds from plant and marine environment. International journal of molecular sciences. 2018 Nov;19(11):3533.
10. Chakraborty A, Brantner A, Mukainaka T, Nobukuni Y, Kuchide M, Konoshima T, Tokuda H, Nishino H. Cancer chemopreventive activity of Achyranthes aspera leaves on Epstein–Barr virus activation and two-stage mouse skin carcinogenesis. Cancer letters. 2002 Mar 8;177(1):1-5.
11. Balasenthil S, Ramachandran CR, Nagini S. Prevention of 4-nitroquinoline 1-oxide-induced rat tongue carcinogenesis by garlic. Fitoterapia. 2001 Jun 1;72(5):524-31.
12. Greenwell M, Rahman PK. Medicinal plants: their use in anticancer treatment. International journal of pharmaceutical sciences and research. 2015 Oct 1;6(10):4103.
13. Prakash OM, Kumar A, Kumar P. Anticancer potential of plants and natural products. Am J Pharmacol Sci. 2013;1(6):104-15.
14. Desai AG, Qazi GN, Ganju RK, El-Tamer M, Singh J, Saxena AK, Bedi YS, Taneja SC, Bhat HK. Medicinal plants and cancer chemoprevention. Current drug metabolism. 2008 Sep 1;9(7):581-91.
15. Madhuri S, Pandey G. Some anticancer medicinal plants of foreign origin. Current science. 2009 Mar 25:779-83.
16. Shoeb M. Anti-cancer agents from medicinal plants. Bangladesh journal of pharmacology. 2006;1(2):35-41.
17. Newman DJ, Cragg GM. Natural products as sources of new drugs from 1981 to 2014. Journal of natural products. 2016 Mar 25;79(3):629-61.
18. Galon J, Bruni D. Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. Nature reviews Drug discovery. 2019 Mar;18(3):197-218.

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Overview

Plant as A Source of Medicine: A Contemporary Overview

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INTRODUCTION

Medicinal plants are various plants used in herbalist and thought by some to have medicinal properties**.** The definition of Medicinal Plant has been formulated by WHO (World Health Organization) as follows- "A medicinal plant is any plant which, in one or more of its organ, contains substance that can be used for therapeutic purpose or which is a precursor for synthesis of useful drugs."

The plants that possess therapeutic properties or exert beneficial pharmacological effects on the animal body are generally designated as "Medicinal Plants". Although there are no apparent morphological characteristics in the medicinal plants growing with them, yet they possess some special qualities or virtues that make them medicinally important. It has now been established that the plants which naturally synthesis and accumulate some secondary metabolites, like alkaloids, glycosides, tannins, volatiles oils and contain minerals and vitamins, possess medicinal properties. Medicinal plants constitute an important natural wealth of a country. They play a significant role in providing primary health care services to rural people. They serve as therapeutic agents as well as important raw materials for the manufacture of traditional and modern medicine. Substantial amount of foreign exchange can be earned by exporting medicinal plants to other countries. In this way indigenous medicinal plants play significant role of an economy of a country. Plant containing active chemical constituents in any of its part or parts like root, stem, leaves, bark, fruit and seed which produces a definite curing physiological response in the treatment of various ailments in humans and other animals is termed as medicinal plant. The various chemicals work together to reach equilibrium in the body as they do in the plant, and so produce gentle progressive healing within the body tissues.

PHYTOMEDICINE IN GLOBAL HEALTH CARE

Plants have been the basis of many traditional medicine systems throughout the world for thousands of years and continue to provide mankind with new remedies. Plant-Based medicines initially dispensed in the form of crude drugs such as tinctures, teas, poultices, powders, and other herbal formulations, now serve as the basis of novel drug discovery **.** Phytomedicine, popularly

known as herbal medicine, refers to the use of plant seeds, berries, roots, leaves, bark, or flowers for medicinal purposes. It has long reputation as "the people's medicine" for its accessibility, safety and the ease with which it can be prepared. According to World Health Organization (WHO), from 119 plant-derived medicines, about 74% are used in modern medicine in ways that correlate directly with their traditional uses. WHO also estimates that 4 billion people, 80% of the world's population, presently use herbal medicine for primary health care. Herbal medicine is a common element in Ayurvedic, Homeopathic, Naturopathic, Traditional oriental, Native American and Indian medicine. Even among prescription drugs, at least 25% contain at least one compound derived from higher plants. The percentage might be higher if we include over-the-counter (OTC) drugs.

In developing countries including Bangladesh, about 75% of the populations rely on different forms of traditional medicine for their primary health care. The high cost of imported conventional drugs and/ or inaccessibility to western health care facility, imply that traditional mode of health care is the main form of health care that is affordable and available to our rural people. On the other hand, even when western health facilities are available, traditional medicine is viewed as an efficient and an acceptable system from a cultural perspective. As a result, traditional medicines usually exist side-by-side with western forms of medicine.

NATURAL PRODUCT RESEARCH AND DRUG DISCOVERY

Nature appears to be a therapeutic cornucopia to treat superfluity of diseases ranging from common cold to multifarious type of illness since the dawn of civilization. Overwhelming evidence has accumulated showing that natural products from plants, microorganisms and marine organisms comprise major portion of the total repertoire of the available therapeutic drugs. Products of natural origins are often called ''natural products.''

Natural products include: an entire organism (e.g., a plant, an animal, or a microorganism) that has not undergone any kind of processing or treatment other than a simple process of preservation (e.g., drying), part of an organism (e.g., leaves or flowers of a plant, an isolated animal organ), an extract of an organism or part of an organism, and exudates, and pure compounds (e.g., alkaloids, glycosides, sugars, flavonoids, coumarins, lignans, steroids, terpenoids, etc.) isolated from plants, animals, or microorganisms . However, in most cases the term natural products refer to secondary metabolites, small molecules (mol wt. <2000 amu) produced by an organism that are not strictly necessary for the survival of the organism.

Natural products have played a key role in drug discovery research, as many medicines are either natural products or derivatives thereof. Indeed, it is estimated that about 40% of all medicines is either natural products or their semi-synthetic derivatives. This may not be surprising as herbal medicine is a tradition of healthcare since ancient times and natural extracts screening has been one of the roots of drug discovery research, where erythromycin and rifampicin (bacterial infections), statins (hyperlipidemia), quinines and artemisinin (malaria), paclitaxel, vinblastine and

vincristine (cancer), are a few well-known natural products-based medicines.

For bacterial infections, over 80% of all medicines in clinical use is either natural products or their derivatives, while for anti-cancer agents over 60% of all drugs is either natural products or derivatives thereof; examples of several potential lead molecules are vincristine, vinblastine, taxol, camptothecin, podophyllotoxin, combretastatins, etc which have been isolated from plants for successful use in cancer treatment .In earlier times, all drugs and medicinal agents were derived from natural substances, and most of these remedies were obtained from higher plants. Today, many new chemotherapeutic agents are synthetically derived, based on "rational" drug design. The study of natural products has advantages over synthetic drug design in that it leads optimally to materials having new structural features with novel biological activity. Not only do plants continue to serve as important sources of new drugs, but photochemical derived from them are also extremely useful as lead structures for synthetic modification and optimization of bioactivity. The starting materials for about one-half of the medicines we use today come from natural sources. Virtually every pharmacological class of drugs includes a natural product prototype. The future of plants as sources of medicinal agents for use in investigation, prevention, and treatment of diseases is very promising.

TRADITIONAL MEDICINE

Traditional medicine (also known as **indigenous or folk medicine**) comprises unscientific knowledge systems that developed over generations within various societies before the era of modern medicine. Practices known as traditional medicines include herbal, Ayurveda, Siddha medicine, Unani, ancient Iranian medicine, Islamic medicine, traditional Chinese medicine, traditional Korean medicine, acupuncture, Muti, Ifá, traditional African medicine, and other pseudo medical knowledge and practices all over the globe. It may include formalized aspects of folk medicine, i.e. longstanding remedies passed on and practiced by lay people.

Botánicas such as this one in Jamaica Plain, Massachusetts cater to the Latino community and sell folk medicine alongside statues of saints, candles decorated with prayers, lucky bamboo, and other items.

The World Health Organization (WHO) defines traditional medicine as:

"The health practices, approaches, knowledge and beliefs incorporating plant, animal and mineral-based medicines, spiritual therapies, manual techniques and exercises, applied singularly or in combination to treat, diagnose and prevent illnesses or maintain well-being."

In some Asian and African countries, up to 80% of the population relies on traditional medicine for their primary health care needs. When adopted outside of its traditional culture, traditional medicine is often called complementary and alternative medicine. Herbal medicines can be very lucrative, generating billions of dollars in sales, but adulteration or counterfeit herbs can also be a health hazard. The WHO also notes, though, that "inappropriate use of traditional medicines or practices can have negative or dangerous effects" and that "further research is needed to ascertain the efficacy and safety" of several of the practices and medicinal plants used by traditional medicine systems. Core disciplines which study traditional medicine include ethno medicine, ethno botany, and medical anthropology.

Safety of traditional medicine

Traditional medicine includes many different practices and remedies, and varies from one country to another. While some practices seem to offer benefits, others remain questionable.

In 2002, WHO launched a strategy on traditional medicine to help countries explore its potential for people's health and well-being, while minimizing the risks of unproven or misused remedies.

The main aim of the strategy is to encourage further research.

There is some evidence that seems to support the use of traditional and complementary medicine – for example, acupuncture in relieving pain, yoga to reduce asthma attacks, and tai ji techniques to help elderly people reduce their fear of falls. WHO does not currently recommend these practices, but is working with countries to promote an evidence-based approach to addressing safety, efficacy and quality issues.

Unfortunately, the misuse of certain herbal remedies can cause harm – even death – in some cases. The herb Ma Huang (ephedra) is traditionally used in China to treat short-term respiratory congestion. In the United States of America, the herb was marketed as a dietary aid, whose long-term use led to at least a dozen deaths, heart attacks and strokes.

In Belgium, at least 70 people required renal transplants or dialysis for interstitial fibrosis of the kidney after taking the wrong herb from the Aristolochiaceae family, again as a dietary aid.

In developing countries, where more than one-third of the population lack access to essential medicines, the provision of safe and effective traditional and alternative remedies could become an important way of increasing access to health care. One way to ensure this is to integrate traditional medicine into the formal health system, thus ensuring better safety and adequate follow-up for patients.

Traditional medicine is also becoming more popular in industrialized countries, where many products can be bought over the counter. In addition to concerns over safety and quality issues, traditional medicine also raises questions of protecting biodiversity (through over harvesting of the raw material for herbal medicines and other products), and protecting the traditional knowledge of communities.

Importance of traditional medicine

WHO gives great importance and value to Traditional Medicine practices, particularly in Countries where this type of care is fundamental part of the people's culture.

-Traditional Medicine is a "global" term used both in relation to TM systems (Chinese, Indian Ayurveda, Arabic Unani and so on) and various forms of indigenous medicine worldwide. TM includes therapies that involve use of drugs based on plants, animal and/or mineral parts, as well non-drug therapies such as in the case of acupuncture, manual and spiritual therapies. In Countries where the health system is predominantly based on allopathic or where TM has not been incorporated into the national health system, this type of therapy is often called "complementary", "alternative" or "unconventional" medicine.

-The use of the TM is widespread and its importance on health and economic level is growing. In Africa, up to 80% of the population uses TM to meet its health care needs. In Asia and Latin America, populations continue use TM because of historical circumstances and cultural beliefs; only to make an example, in China, TM is

40% of overall health care performances in the Country.

At the same time, in many developed Countries, TM gains a lot in popularity and the percentage of population that has used this type of therapy at least one-time during life is 48% in Australia, 70% in Canada, 42% in United States, 38% in Belgium and 75% in France.

-In many parts of the world, the expenditure for TM are very consistent and rapidly increasing. As example, in Malaysia is estimated that 500 million dollars are spent each year for this type of health care, while only 300 millions are spent at the same time for allopathic. Also other Countries, as UK, USA and Australia do not spend less than 80 million dollars each year for TM.

-In developing Countries TM is highly diffused because this type of health care is very accessible and affordable, and there is a lot more traditional practitioners than doctors (if we consider the example of Uganda, we note that the number of traditional practitioners is 1/2000 or 1/4000 persons, while conventional doctors are 1/20000 at least).

-TM is very used especially in rural areas, where conventional medicine often cannot arrive, then population consider TM the only possibility to have access to health care in the biggest part of developing world. The costs are lower than conventional drugs and another key aspect is related to the fact that TM means considering the body as inseparable from the soul, and then this holistic approach is also very appreciated in developed Countries.

- Traditional medicine involves some aspects of mind-body interventions and use of animal-based products, it is largely plant-based.

-Conventional medicine focuses on experiment and disease-causing pathogens. Traditional medicine however postulates that the human being is both a somatic and spiritual entity, and that disease can be due to supernatural causes arising from the anger of ancestral or evil spirits, the result of witchcraft or the entry of an object into the body. It is therefore not only the symptoms of the disease that are

-Traditional healers utilize a variety of approaches to diagnose, treat or prevent illness.

CONCLUSION

The traditional pharmacopoeia of the Reang ethnic group incorporates a myriad of diverse flora available locally. Traditional knowledge of the remedies is passed down through oral traditions without any written document. This traditional knowledge is however, currently threatened mainly due to acculturation and deforestation. Therefore, documenting medicinal plants and associated indigenous knowledge can be used as a basis for developing management plans for conservation and sustainable use of medicinal plants of the study area. In addition, findings of this study can be used as an ethnopharmacological basis for selecting plants for future phytochemical and pharmaceutical studies.

REFERENCES

1. Li Y, Kong D, Fu Y, Sussman MR, Wu H. The effect of developmental and environmental factors on secondary metabolites in medicinal plants. Plant Physiol Biochem. 2020;148:80–9.

2. Pant B. Application of plant cell and tissue culture for the production of phytochemicals in medicinal plants. Adv Exp Med Biol. 2014;808:25–39.

3. Shawahna R, Jaradat NA. Ethnopharmacological survey of medicinal plants used by patients with psoriasis in the West Bank of Palestine. BMC Complement Altern Med. 2017;17(1):4.

4. Van Wyk B-E. A family-level floristic inventory and analysis of medicinal plants used in Traditional African Medicine. J Ethnopharmacol. 2020;249(112351):112351.

5. Afolayan AJ, Grierson DS, Mbeng WO. Ethnobotanical survey of medicinal plants used in the management of skin disorders among the Xhosa communities of the Amathole District, Eastern Cape, South Africa. J Ethnopharmacol. 2014;153(1):220–32.

6. Gairola S, Sharma J, Bedi YS. A cross-cultural analysis of Jammu, Kashmir and Ladakh (India) medicinal plant use. J Ethnopharmacol. 2014;155(2):925–86.

7. Shil S, Dutta Choudhury M, Das S. Indigenous knowledge of medicinal plants used by the Reang tribe of Tripura state of India. J Ethnopharmacol. 2014;152(1):135–41.

8. Xavier TF, Kannan M, Lija L, Auxillia A, Rose AKF, Kumar SS. Ethnobotanical study of Kani tribes in Thoduhills of Kerala, South India. J Ethnopharmacol. 2014;152(1):78–90.

9. Seebaluck R, Gurib-Fakim A, Mahomoodally F. Medicinal plants from the genus Acalypha (Euphorbiaceae)--a review of their ethnopharmacology and phytochemistry. J Ethnopharmacol. 2015;159:137–57.

10. Boniface PK, Baptista Ferreira S, Roland Kaiser C. Current state of knowledge on the traditional uses, phytochemistry, and pharmacology of the genus Hymenaea. J Ethnopharmacol. 2017;206:193–223.

11. Guo Y, Yin T, Wang X, Zhang F, Pan G, Lv H, et al. Traditional uses, phytochemistry, pharmacology and toxicology of the genus Cimicifuga: A review. J Ethnopharmacol. 2017;209:264–82.

12. Rokaya MB, Uprety Y, Poudel RC, Timsina B, Münzbergová Z, Asselin H, et al. Traditional uses of medicinal plants in gastrointestinal disorders in Nepal. J Ethnopharmacol. 2014;158 Pt A:221–9.

13. Van Wyk B-E. A review of commercially important African medicinal plants. J Ethnopharmacol. 2015;176:118–34.

14. Ashiq S, Hussain M, Ahmad B. Natural occurrence of mycotoxins in medicinal plants: a review. Fungal Genet Biol. 2014;66:1–10.

15. Bottoni M, Milani F, Colombo L, Nallio K, Colombo PS, Giuliani C, et al. Using medicinal plants in Valmalenco (Italian alps): From tradition to scientific approaches. Molecules. 2020;25(18):4144.

16. Lock O, Perez E, Villar M, Flores D, Rojas R. Bioactive compounds from plants used in Peruvian traditional medicine. Nat Prod Commun. 2016;11(3):315–37.

17. Tansaz M, Memarzadehzavareh H, Qaraaty M, Eftekhar T, Tabarrai M, Kamalinejad M. Menorrhagia management in Iranian traditional medicine. J Evid Based Complementary Altern Med. 2016;21(1):71–6.

18. Jafari S, Abdollahi M, Saeidnia S. Personalized medicine: a confluence of traditional and contemporary medicine. Altern Ther Health Med. 2014;20(5):31–40.

19. Novy JW. Medicinal plants of the eastern region of Madagascar. J Ethnopharmacol. 1997;55(2):119–26.

20. Shankar K, Liao LP. Traditional systems of medicine. Phys Med Rehabil Clin N Am. 2004;15(4):725–47, v.