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HERBAL DRUG ADULTERATION WITH SYNTHETIC PHYTOCONSTITUENTS AND THEIR ANALOGS AS ADULTERANTS A CONUNDRUM IN QUALITY CONTROL OF HERBAL FORMULATIONS: A REVIEW

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Abstract:
Synthetic or chemical analogs adulteration refers to the incorporation of chemical compounds which are identical to naturally existing chemical compounds but differ significantly in chemical properties, behavior, and intent. As there is a lack of analytical techniques for identifying and quantifying phytoconstituents, the development of quality control techniques for herbal products is very important. To date, the Only Carbon dating technique is considered reliable for detecting such synthetic adulterants, which is expensive and difficult to access. The current publication emphasizes the advantages and drawbacks of contamination with synthetic phytochemicals in herbal medications and dietary products. This study also overviews the scarcity of herbal drugs and presently available drug evaluation tests. In conclusion, non-toxicity, efficacy, accuracy, stability, and potency are the ultimate standards for any drug (synthetic or natural). Our review emphasizes the importance of detecting, identifying, and quantifying synthetic phytochemicals, their structural analogs, and impurities found in herbal products.

Keywords: Synthetic analogs, Phytochemicals, Herbal Drug adulteration, Drug evaluation, Impurities, Toxicity.

1. Introduction

Phytochemicals are non-essential nutritional plant-based natural compounds with disease preventive/ protective properties. Many phytochemicals are used as first-line medicines in the pharmaceutical industry. Since most phytochemicals have complex structures, their chemical synthesis is time-consuming, unreliable, and expensive. As a result, phytochemicals are often produced commercially by separating them from their natural hosts. Since the abundance of phytochemicals in growing plants is always insufficient and plants have a complex metabolite history, extracting target phytochemicals from native producers can be quite challenging(J. H. al., 2013). Many chemists have struggled to complete the overall synthesis of these natural products over time. As a result, the ability of medicinal chemists to change or modify one or more atoms, a functional group, or a substructure to give structurally similar substances with more potent behaviors but fewer side effects than the original drug is an immense advancement in medicinal chemistry. A synthetic analog is a chemical compound that has similar chemical properties to a naturally occurring compound but is generally structurally different from that chemical compound. Since they are artificially engineered versions of conventional products, they are often referred to

as "designer drugs." An analogy is either a practical or a structural analog to the field of pharmacology. A functional analog is a chemical compound with properties (physical, chemical, biochemical, or pharmacological) identical to those of the natural compound. In contrast, a structural analog chemical compound with a significantly different chemical structure from one another. Natural product vulnerability and the urge for more potent drugs have pushed the synthesis of various functional analogs to a greater height (Egbuna et al., 2019).

According to sources, herbal remedies are recently adulterated with undeclared prescription drugs or their structurally adapted analogs. Many other western herbal medicinal drugs have been confirmed to be laced with various forms of unidentified synthetic chemicals with different pharmacological actions, nutritional supplements, and sexual stimulants. Herbal and conventional medicines can contain various pharmacologically active chemicals extracted from different parts of plants. As a result, if the suppliers are deceptive, it is not easy to monitor how many chemicals are used in preparation. Furthermore, conventional, and herbal remedies and supplements have not been extensively scientifically tested for long-term efficacy, medication interactions, etc.(Skalicka-Woźniak et al., 2017).

2. History of Herbal Drugs and Their Importance, Causes of Scarcity and Adulteration

In India, Ayurveda is the ancient and holy health care system that originated 5000 years ago, over the last century, chemically synthesized drug manufacturing and development have increased in health care worldwide. However, developing countries are now increasingly using herbal medicines for primary health care because of their affordability and cultural acceptability, receptivity to the human body, ease of access, and minimal side effects (Rafieian-Kopaei & Sewell, 2014). 70% of the Indian population depends on conventional medicine for their health care needs(Wachtel-Galor & Benzie, 2011).

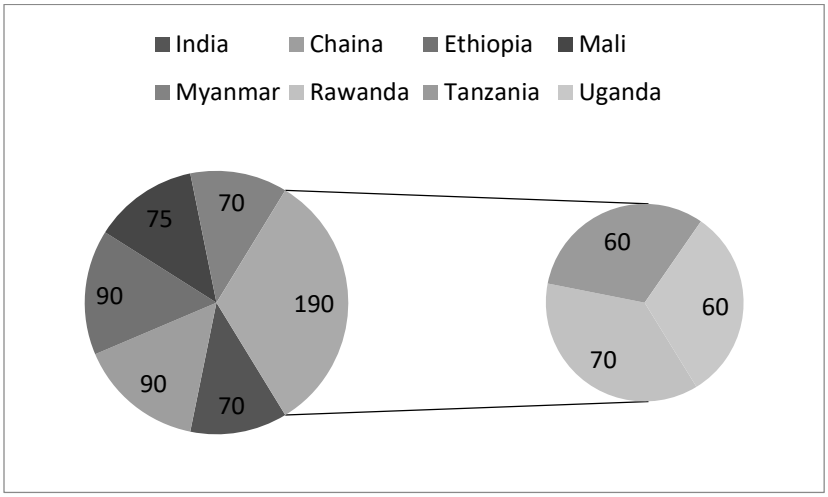

Figure.01: Proportion of Developing countries utilizing Herbal medicines for health ailments

The above data indicates the percentage of herbal drug usage in developing nations. About 90% of the Chinese and Ethiopian population depend on herbal drugs for primary health care, and 60-70 % of the African countries like Uganda, Tanzania, and Rwanda also rely on plant-based medicine. 70 % of the Indian population believes in alternative systems of medicine. The

government of India also promotes the use of herbal medicines through the Ministry of Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy (AYUSH) (J. H. al., 2013)

As therapeutic plants gain scientific and economic appeal, the wild native species from which most medicinal plants are grown are under threat. Many therapeutic plants have been overharvested, threatening their extinction. Experts predict that Earth loses at least one new drug candidate every two years. To overcome this obstacle, organizations and governments worldwide are rising to the occasion(Chen et al., 2016). Reasons for the extinction of herbal drugs are Habitat destruction, Environmental factors (rainfall, deforestation, siltation of water bodies, lack of pollinators), Developmental Activities (submersion, infrastructure activity), Bioprospecting, Agriculture & forestry methods, and Overharvesting(Figueiredo & Grelle, 2009; Wagh & Jain, 2015).

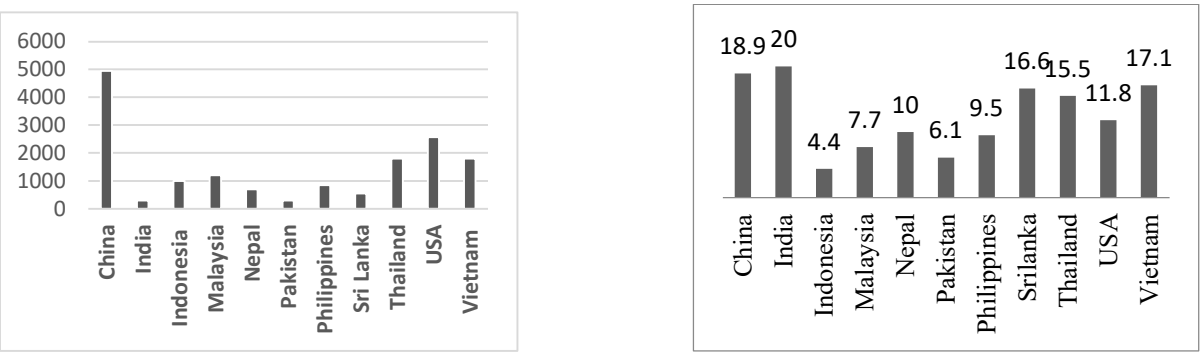

Figure.02: Percentage and number of medicinal plant species (J. H. al., 2013)

Due to excessive demand and shortage of natural product manufacture in the market and the extinction of medicinal plants across the globe, Herbal medications have been contaminated with a variety of adulterants. There are many types of research done regarding herbal adulteration, the basic definition of Adulteration is "partially or wholly replacing an original crude medication with a resembling material that is either devoid of or inferior in chemical and therapeutic quality. Adulterants are typically substandard or sub-standard equivalents of crude medication or artificially produced goods"(Professor et al., 2017). There are different types of Drug adulterations in the present market, these include Substitution with substandard commercial varieties, Substitution with inferior drugs that are superficially similar, Substitution with artificially manufactured substances, Presence of vegetative matter, Adulteration of powders, and Presence of Harmful adulterants.

Several factors entice the public's interest in herbal medicine including an infinite number of claims on the effectiveness and efficacy of plant medicines, consumer preference for natural therapies and greater interest in alternative medicine, patient's erroneous belief in herbal products, believing them superior to allopathic medicine, consumers dissatisfaction with the use of conventional pharmaceuticals that are expensive and have unprecedented side effects and patient's mistrust of physician's incorrect diagnoses and failure to identify problems, leads them to seek alternative treatment options such as herbal medicine rather than self-medication.

Presently, multiple companies in India produce various herbal formulations under different brand names prescribed for acute and chronic ailments. **Table .01** lists a few herbal industries manufacturing and marketing herbal medicines in India.

S.NO	Company Name	Brand Name	Major Active Constituent	Uses
01	Aimil Pharmaceuticals (India) Ltd.	Ashree Forte Capsules	Asoka Bark	A restorative tonic for men
02	Ajmera Pharmaceutical Pvt. Ltd.	Alargin Forte Capsules	Ext.Tejpatra	Food allergy, Mild urticaria, and Dermato graphism
03	Alarsin Pharmaceuticals	Aluretic Tablets	Daruharidra	Increased blood pressure, Congestive heart failure, Nephritis, renal insufficiency
04	Ban Labs Pvt. Ltd.	Calcurosin Syrup	Nimbak Sat	Dissolves and expels calculi
05	BDH Industries	FTX Tablets	Commiphora Mukul	Reduces excess fat
06	Charak Pharmaceuticals (India) Ltd.	Gulkand	Gulkand	Cooling Agent
07	Concept Pharmaceutical Ltd.	Kaskol Cough Syrup	Adhatoda vasica	Upper respiratory tract infections
08	Dabur India Ltd.	Chyawanprash Avaleha	Amla Green	Protecting everyday infections
09	Deccan Ayurvedashram Pharmacy	AG Forte Avaleha	Ashwagandha	General weakness
10	Deys Medical Stores Ltd.	Herbodil Liquid	Vasaka	For Choked voice, Cough, and Sore throat
11	Everest Herbal Remedies	Asmocline Capsules	Piper Longum	Bronchial Asthma
12	Growel Pharmaceuticals	Dermex Capsule	Gandhak Rasayan	Psoriasis
13	Hamdard Laboratories	Zulamla Hair Tonic	Amla	Anti-hairfall

14	Herbals Private Ltd.	Heart soothing Liquid	Terminalia Arjuna	Pericarditis, Angina
15	Indian Herbs Research & Supply Co. Pvt. Ltd	Himalayan Batista	Manthapak	Constipation, Antibacterial
16	Jain Ayurvedic Pharmacy	Janodine	Sunthi	Good health & Energy
17	Jawahar Chemicals Pvt Ltd	Sisairosp	Coconut oil	Psoriasis
18	Jupiter Pharmaceutical Ltd	Carminozyme Liquid	Triphala	Carminative Liver disfunction
19	Karnataka Antibiotics & Pharmaceuticals Ltd.	Exol Syrup	Bhringaraja	Jaundice, Cirrhosis of Liver
20	Kumar Ayurvedic Trading Co.	Navratna Forte	Shilajit	Strength & Vitality
21	Lucent Pharmaceutical Pvt Ltd.	Herbal Baby massage Oil	Varahi	Rickets
22	Natural Herbal Remedies	Deflamm Capsules	Balasamodendran mukul	Osteo Arthritis
23	Shree baidyanath Ayurved Bhawan Ltd.	Surakta	Indian Sarsaparilla	Skin Problems, Salt-free diet
24	Skap Pharmaceutical Pvt Ltd	Mensuel	Ricinus Communis	Non-Hormonal Mensuration Regulator
25	Spectromed Pharmaceutical Manufacturers	Spec	Dasamoolakwatha Ext.	Anti-tuberculosis, Treatment of Cancer
26	Sri surya Ayurveda Nilayam	Vernika Capsules	Ex. CP	Treatment of piles
27	Swastik formulations Pvt Ltd	Gro liquid	Bhrigaraj	Improves autoimmune system
28	Themis Chemicals Ltd.	Digiped Syrup	Tinospora Cardifolia	Digestion Disorders
29	Trio Pharma	Argone Capsules	Abha Guggul	Neuralgia, Osteoporosis

30	Universal Medicaments Pvt Ltd	Karnim Capsules	Momordica Charantia	Anti-Diabetic

Table.01: Different brands of Commercial Herbal drugs marketed in India (*Natural Medicines Reference Manual : Ayurveda, Siddha, Unani, Homoeopathy*, 1999)

However, natural drugs have many drawbacks, including the fact that they take longer to produce, are more expensive, and may not be as long-lasting as synthetic drugs. Additionally, once isolated from their source, natural chemical compounds may perform differently than intended(Abdel-Aziz et al., 2016; Zhang et al., 2015). Exo interactions (interactions with chemicals do not present in the extract) and endo interactions (interactions between substances present in the extract) can have severe consequences for human health (Trease & E., 2009). The key obstacles impacting drug discovery from natural sources are the isolation and purification of active principles from an extraordinarily complex matrix, and this reductionist approach may result in equivocal clinical trial results(Wachtel-Galor & Benzie, 2011).

Many intentional and unintentional factors that lead to adulteration are the scarcity of drugs, a high price in the present market, the trader's intention to earn more profits, lack of knowledge about authentic sources, morphological similarity, unscientific collection, confusion in vernacular names, while in some cases it may happen accidentally (Professor et al., 2017; Sagar, 2014).

3. Synthetic Adulteration of Herbal Formulations

In addition to the above introduction of synthetic analogs and their adulteration with natural formulations, many pharmacopeias and national formulary had incorporated the monographs for the quality control of their herbal species/ herbal extracts. Quality control investigations have been conducted using herbal biomarkers. Presently these herbal markers are gaining more importance in the countries like India, China, and Historically, herbal medicines have been used in the European Union and are likely the largest exporter. A chemical marker is a key component of a medicinal product that is of interest to the European Medical Agency (EMEA), regardless of whether its constituents act therapeutically. EMEA categorizes these markers into two groups: Analytical markers and Active markers. Many of these active markers are studied for their pharmacological activity and were found to possess potent therapeutic action. Thus, to match the chemical and biological equivalence (Especially during export), the herbal industries are adulterating the drugs/ extracts/ formulations with synthetic analytical/active markers (synthetic analogs). Even Though synthetic analogs have a similar effect as the natural phytoconstituents, they are considered more potent and dangerous, causing severe side effects. In natural herbal medicines, the other substances present may balance the adverse effects caused by the bioactive compounds. For example, the use of novel psychoactive agents containing synthetic cannabinoids is reported to possess severe neuropsychiatric side effects when compared to natural analogs (Welz et al., 2018). (**Table.02)**

S. No	Phytochemical	Pharmacological Activity	Plant	Synthetic Analogue / Derivative
1	Aesculetin	Anti-dysentry	*Fraxinus rhychophylla*	Scopoletin, Isoscopoletin (Maridass & Britto, 2008)
2	Ajmalicine	Anti-hypertensive	*Agrimonia rupatoria*	Yohimbine, rauwolscine (Hartmann et al., 1999)
3	Anabasine	Skeletal muscle relaxant	*Anabasis aphylla*	The structural isomer of nicotine(Maridass & Britto, 2008)
4	Artemisinin	Anti-Malaria	*Artemisia annua*	Artesunate, Artimether, Artilinic Acid (A. M. D. al., 2010)
5	Atropine	Anti-cholinergic	*Atropa bellanoda*	Homatropine, Atropine methonitrate, Methadone, Loperamide (Hey, 2011)
6	Betulinic Acid	Anti-Cancer, Anti-HIV, Anti helmentic	*Betula alba*	Bevirimat (Chowdhury et al., 2002)
7	Caffein	CNS stimulant	*Coffea arabica*	Theophylline, theobromine (Nehlig et al., 1992)
8	Camptothecin	Topoisomerase inhibitor	*Camptotheca acuminate*	Topotecan, irinotecan (Krueger, 2005)
9	Capsaicin	Anti-analgesic	Solanaceae Family	Dehydrocapsaicin, norhydro capsaicin, homo capsaicin (Fattori et al., 2016)
10	Castanospermine	Potent inhibitor of glucosidase enzymes	*Castanospermum australe*	Celgosivir (Saul et al., 1985)
11	Cocaine	Local anesthetic	*Erythroxylum coca* Lam	Alpha eucaine, niravanine, amylococaine, prococane, betacocaine (Balunas & Kinghorn, 2005)
12	Codeine	Used to treat pain	*Papaver sominiferum*	Nico codeine, iso codeine (Prommer, 2011)

13	Combretastatin	Vascular disruption in tumours	*Combretum caffrum*	Ombrabulin (Pettit et al., 1987)
14	Curcuminoids	Antioxidant	*Curcuma longa*	Demethoxy curcumin, bismethoxy curcumin (Jayaprakasha et al., 2006)
15	Cytisine(alkaloid)	Smoking cessation	*Cytisuslaburnum* L.	Varenicline (N. W. al., 2014)
16	Dicoumarol	Used along with heparin for the treatment of deep venous thrombosis	*Penicillium, Aspergillus*, *Fusarium*,	A prototype of Phenindione, ethyl biscoumacete, tesicam, piroxicam(Kresge et al., 2005)
17	Digitoxin	Cardiotonic	*Digitalis purpurea* L.	Digitoxigenin, (Wagner & Kenreigh, 2007)
18	Digoxin	Cardiotonic	*Digitalis lanata Ehrh*	Acetyldigoxin(Wagner & Kenreigh, 2007)
19	Emetine	Anti-protozoal and Antiemetic	*Cephaelisipecacuanha*	Cephaeline, dehydro emetine (Akinboye et al., 2012)
20	Enoxolone	Treatment of peptic ulcers	*Glycyrrhiza glabra*	Carbenoxalone sodium (Connors, 2012)
21	Ephedrine	Used to prevent low blood pressure During spinal anesthesia.	*Ephedrasinica*	Amphetamine, methylphenidate, dexamphetamine (Bagchi & Preuss, 2007)
22	Genistein	Antioxidant, Anticancer	*Glycinemax* Merr	Phenoxodiol (Si et al., 2007)
23	Indirubin	Used for chronic myeloid leukemia treatment	*Indigonaturalis*	Meisoindigo (Nirmala et al., 2011)
24	Khellin	For treating renal colic, bronchial asthma	*Ammi visnaga*	Benzarone, benziodarone, amiodarone, nedocromil (Shinde & Laddha, 2014)
25	Lobeline	Respiratory stimulant	*Lobelia* spp.	Lobelanidine, Lobelanine (Stead & Hughes, 2012)

26	Papaverine	Antispasmodic, treatment of acute mesenteric ischemia	*Papaversomniferum* L.	Eupaverin, ethaverine, mebeverine, verapamil(Cymerman-Craig et al., 1955)
27	Physostigmine	A reversible cholinesterase inhibitor. Anantidote for *Atropa belladonna* poisoning	*Physostigma venenosum*	Miotine, neostigmine, pyridostigmine (Roberts, 2016)
28	Podophyllotoxin	Topical antiviral agent	*Podophyllum peltatum*	Podophyllotoxin, benzylidene glucoside, teniposide, etoposide (Canel et al., 2000)
29	Protopanaxadiol	Anticancer	*Panax ginseng*	Protopanaxatriol, Panaxatriol (Nirmala et al., 2011)
30	Quinine	Used to treat malaria	*Cinchona* spp.	Chloroquine, primaquine, mefloquine, quinine bisulfate

Table.02: Phytochemicals and their synthetic analogs/derivatives

4. Synthetic Adulteration of Phytochemicals: A Potential Threat

Herbal treatments can be considered healthy without side effects, but many impurities have been identified despite being marketed as herbal. There has been a significant public health issue related to the adulteration of herbal slimming preparations with synthetic compounds, which has led to arguments against uncontrolled herbal treatment. In most cases, PDE-5 antagonists such as Sildenafil citrate, vardenafil hydrochloride, and tadalafil, as well as their analogs obtained by slight modifications of the major molecular structures, are used. PDE-5 inhibitors, which are not analogs of licensed drugs and have a new form of system among illicit erectile dysfunction compounds, have been found in some cases. Benzamidenafil, structurally unrelated to sildenafil, vardenafil, and tadalafil, has been found in a natural herbal supplement in Singapore (L. B.-T. al., 2004). Since new analogs are challenging to identify during any regulation, it is ubiquitous for established structures to be modified. Such analog adulterants are much more harmful. Since they are structurally similar to the parent drug, they can maintain similar pharmacological activities or have marginally or entirely different properties. Their safety and toxicology profiles are often uncertain due to the lack of clinical trials(Skalicka-Woźniak et al., 2017).

4.1 Synthetic Caffeine: Caffeine is often applied to diet and herbal products as methylxanthine derivatives and adrenergic stimulants because of its soothing and thermogenic impact(C. V. al., 2018). Many weight-loss products contain high levels of caffeine from synthetic sources to improve thermogenesis and lipid metabolism. The effects of caffeine on resting energy consumption in adult humans (both normal and overweight) have been demonstrated to be dose-

dependent. Caffeine stimulates adenosine receptors and inhibits phosphodiesterase, which increases metabolic rate. This will result in an aggregation of 3, 5-cyclic-adenosine monophosphate in the cells, which is metabolically excitatory. The average human can consume 400 mg of caffeine daily except for pregnant mothers(Roberts, 2016). Caffeine in high doses (>600 mg/day) can cause insomnia, heart palpitations, anxiety, nausea, vomiting, high blood pressure, muscle twitching, tremors, and high cholesterol levels(Cannon et al., 2001).

4.2 Synthetic Methyl Salicylate: The bulk of wintergreen essential oil comprises methyl salicylate, which can be quickly substituted or reduced with synthetic methyl salicylate. The Kolbe-Schmitt reaction, a classic simple organic chemistry reaction, is used in the industrial development of methyl salicylate. The procedure is carried out at high pressures and temperatures, producing high yields of nearly pure salicylic acid(Tournebize et al., 2017). Methanol can be used to methylate salicylic acid, yielding methyl salicylate. Synthetic methyl salicylate behaves as a colorless liquid with a strong wintergreen taste, much as its natural equivalent. Chemically, synthetic methyl salicylate has trace impurities in it that can pose a danger. However, natural methyl salicylate has a difference in the minor constituents, which is why it differs from synthetic methyl salicylate. (Hall & Degenhardt, 2009).

4.3 Synthetic Cannabinoids: Synthetic cannabinoids containing novel psychoactive substances have recently begun to be used recreationally, especially by young adults(Castaneto et al., 2014; Gunderson et al., 2014). Compared to the downturn in the use of many novel psychoactive Substances, including cathinone and piperazines, the number of Synthetic Cannabinoid users is increasing(Tournebize et al., 2017). While synthetic cannabinoid drugs imitate the psychotropic effects of cannabis, their side effects are more volatile and severe. While cannabis-based drugs have been controversial for some time, there is an increasing interest in their therapeutic potential. Repeated sensitivity to cannabinoid agonists, whether organic or synthetic, have been related to harmful physical and psychological outcomes. The most well-known psychiatric side effects are mental diseases, such as bipolar states, dementia, and affective disorders. Synthetic cannabinoid medications are linked to severe harmful psychological and medical problems, according to mounting evidence (Hall & Degenhardt, 2009; Seely et al., 2012; Weinstein et al., 2017).

4.4 Cocaine: Cocaine is a naturally occurring and illegally obtained psychostimulant substance that acts on monoaminergic neurotransmitter transporters. Oliver Kudlacek et al. (2017) reviewed illegal street cocaine and its adulterants such as Levamisole and aminorex. Since a subset of these adulterants has been discovered to have effects comparable to cocaine itself, these adulterants' increases in monoamines are also the fundamental cause of the development of addiction and a variety of severe adverse effects(Kudlacek et al., 2017).

4.5 Synthetic cathinones: Synthetic cathinones are psychoactive compounds that have been synthesized to replicate the stimulating effects of containing natural plant-based cathinone. Through the practice of chewing the leaves of Khat (native to east Africa), people have been engrossed in cathinone-containing substances for several millennia(Numan, 2004). Chicora F. Oliver et al. (2018) reviewed natural cathinones and their synthetic adulteration with 3,4-

methylenedioxymethamphetamine or ecstasy (MDMA) and the review also stated that a series of modifications of the parent compound led to abuse-prone compounds, such as amphetamine-like 4-methyl methcathinone (4-MMC "mephedrone") and 3,4 methylenedioxypyrovalerone (MDPV), and empathogenic agent 3,4 methylenedioxymethcathinone (MDMC) that resembles MDMA in structural terms (Oliver et al., 2019)

5. Present available analytical methods & ways to Overcome Adulteration

Radiocarbon dating was developed at the University of Georgia to detect such adulteration using an analytical method. This is a technique for determining the age of carbon-based compounds derived from living organisms. Age may be determined by calculating the volume of carbon-14 in a sample and comparing it to a globally accepted reference value. Since herbal drugs are not readily available and are therefore expensive, carbon dating has not been conducted on them. Hence there is an urge to develop simple, rapid, accurate, and cost-effective analytical methods such as LC-MS/MS and HPLC to extract, detect, classify, and quantify impurities in herbal medicine synthetic equivalents (Zuo & Lu, 2019). (**Figure.03**)

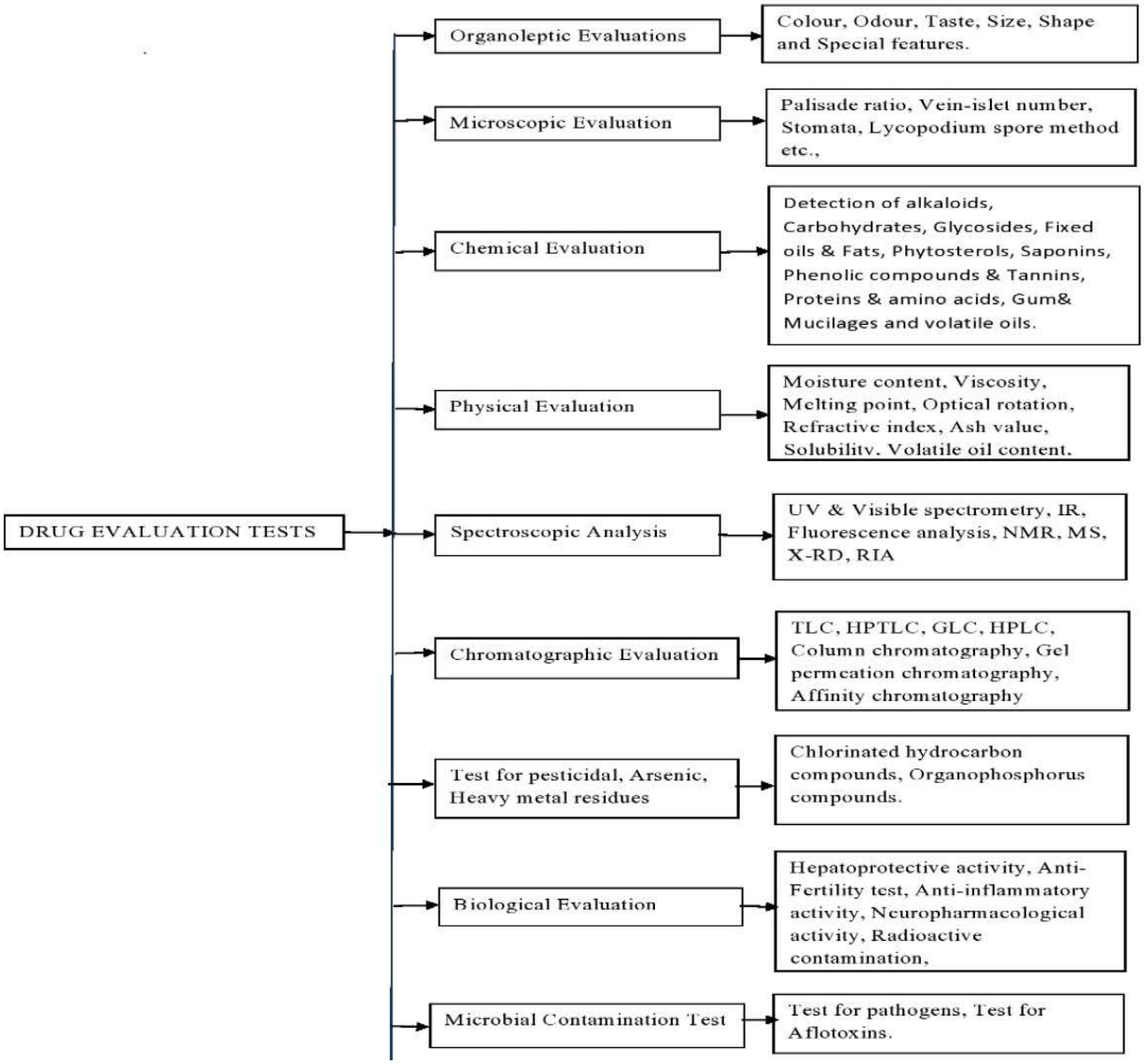

Figure.03: Different existing Drug Evaluation tests at one glance (Mukherjee, 2019)

6. Conclusion:

Herbal medicines are generally considered harmless, safe, and without toxic side effects than prevalent synthetic drugs. Basically, the goal of the present article is to illustrate how crucial quality control for herbal formulations is and the importance of analytical techniques for the detection, isolation, collection, and identification of synthetic analogs as impurities of natural phytochemicals is necessary.

Our study of synthetic analog adulteration with herbal drugs is limited due to insufficient research and data on this topic. In recent years, scientists and researchers have found a number of herbal products that have been adulterated with synthetic chemicals, including weight loss products with Sildenafil citrate, vardenafil hydrochloride, and tadalafil, and antipsychotic compounds with

cannabinoids, cocaine, and cathinone. Various scientific studies have found that pharmaceutical active ingredients have been observed in anti-diabetic, anti-cancer, and natural sexual enhancer products as adulterants. To date, there is no such technique that can identify, isolate, and characterize the synthetic analog adulteration and complete separation of natural and synthetic phytochemicals present in the herbal formulations, except the carbon dating technique (with some major limitations).

In conclusion, non-toxicity, efficacy, accuracy, stability, and potency are the ultimate standards for any drug (synthetic or natural). Concerning the safety of herbal formulation usage and public health, the fundamental goal of this study is to emphasize the importance of a basic analytical approach for detecting synthetic analogs isolation, identification, characterization, and quantification of impurities in herbal medicines sold for different disease treatments.

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Competing Interests:

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