Feature

Pitfalls in Journey from Traditional to Modern Medicine

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Abstract

For thousands of years, man has sought healing powers from the natural world especially from plants. With the advent of modern medicine humans started isolating the active components and used them as such or made more effective analogs for therapy. Crude extract(s) based traditional medicine, on the other hand has better compatibility with the human body with minimal side effects. It is evident that crude extract has lesser side effects because of the modulatory activity of some components present in it along with the active component, which neutralizes the side effects and even synergies the medicinal effects of the later. In this article authors have analyzed the advantages of the use of crude extract than their active component or synthetic counterpart based on information in literature.

Keywords: Traditional medicines, Modern medicines, Crude extracts, Synthetic compounds.
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Introduction

It has been confirmed by WHO that traditional medicines, based largely on different species of plants and animals, serve the health needs of large number of people; especially for millions of people in the vast rural areas of developing countries1, 2. Two hundred and fifty years ago there were few or no synthetic medicines and species of higher plants were the main source of medicines for the world3. The method of discovery of medicines was probably trial and error that related the cause-and-effect relationship to the use of the plant or animal part and a desired result. They used the whole plant or some part of the plant (leaves, bark, roots, seeds and fruits), animals, their organs and glands for the therapeutic purpose, e.g., cinchona bark, digitalis leaf, ephedra aerial parts, poppy capsule, hog testes, etc4.

Many of the drugs we use today are based on folk remedies and subsequent ethnopharmacological studies. There are more than 100 drugs of known structure that are extracted from higher plants and used in allopathic medicine5, 6. More than hundred years old drugs like morphine, digitalis and atropine are the time honoured remedies.

Further, pharmaceutical preparations were discovered that were solid or aqueous, alcoholic or hydroalcoholic fluid extracts of soluble plant or animal constituents. During this period, the use of plants and animals or their parts were abandoned for the more concentrated extracts. Different pharmaceutical dosage forms or preparations were originally designed to extract and concentrate the active drug principles like alkaloids, glycosides and volatile oils primarily from plants and used for therapy4. These preparations greatly decreased the dosage amount and showed increased therapeutic effects. These preparations were in the crude forms of plant or animal material and the main types of these preparations are described as below:

Aromatic waters — Saturated solutions of volatile plant oils or other volatile substances in water, e.g., rose water.

Decoctions — Soluble principles of plant or animal parts extracted with boiling water, e.g., Terminalia decoction.

Elixirs — Aromatic and sweetened hydroalcoholic liquids that contain one or more ingredients, e.g., cinchona alkaloid elixir.
Extracts — These are primarily semisolids or solids obtained by extracting the active principles from plant or animal parts with a suitable solvent and allowing the solvent to evaporate, e.g., belladonna and liver extract.

Fluid extracts — Alcoholic or hydroalcoholic extracts from plant principles in which 1 ml of fluid extract is obtained from 1 g of plant, e.g., gelsemium fluid extract.

Infusions — Soluble plant principles extracted by soaking the plant in hot water, e.g., digitalis infusion.

Liniments — Liquid preparations containing drug(s) applied to the skin with rubbing, e.g., camphor and belladonna liniment.

Mixtures — Aqueous suspensions intended for oral administration that contain insoluble drug(s).

Ointments — Semisolid preparations of drug(s) in a greasy base that liquefy after application to the skin.

Powders — Solid mixtures of finely powdered drugs intended for oral use.

Tinctures — Alcoholic or hydroalcoholic extracts made from 10 to 20 g of dried plant per 100 ml, e.g., tincture of belladonna.

As modern science came up and technology advanced, people started looking for the active components involved in the therapy from the crude extract and with the technology available, tried to purify the active components and use them directly, in higher concentration for the treatment of various diseases. The first major discovery was made by the German pharmacist Serturner (1805), who isolated the narcotic alkaloid morphine from opium, an exudate from the poppy plant. Other discoveries include the isolation of strychnine (1818) from *Strychnos nux-vomica* Linn., quinine (1820) from *Cinchona* bark, codeine from opium and the isolation of antibiotics from mold growth, ephedrine from *Ephedra sinicia* and reserpine from *Rauwolfia serpentina* Benth. ex Kurz. Cod liver oil, epinephrine, levothyroxine, insulin and vasopressin are examples of selected drugs that are obtained from animals.

A big turning point in the history of medicine occurred when people started using modified (semi-synthetic) isolated active drugs from living sources, which involved chemical modifications of drugs derived from plants and animals. The narcotic alkaloids of opium and the solanaceous alkaloids of the nightshade family are examples of plant prototype drugs that were subjected to exhaustive chemical modifications. Some researchers in the first half of the twentieth century attempted to increase the analgesic properties and decrease the addiction liability of morphine by synthesizing thousands of modified semi-synthetic analogs of the opium alkaloid like desomorphine, diacetylmorphine (heroin), dihydrocodeine, ethylmorphine (dionin), hydromorphone (dilaudid), oxymorphone (numorphan), etc. Semi-synthetic derivatives of solanaceous alkaloids of the nightshade family (belladonna, hyoscyamus, stramonium) include anisotropine methylbromide (valpin), eucatropine, homatropine methylbromide (mesopin) and methscopamine bromide (pamine).

Taking enough experience from the use of natural medicines or their modified versions people started synthesizing medicines chemically. During the decade of the 1950’s, the accelerated development of synthetic drugs began and today almost all of the currently used drugs are obtained from pharmaceutical plants. Selected categories of drugs (that contain many specific drugs) include: alkylating agents, angiotensin II antagonists, bile acid sequestrants, benzodiazepines, calcium blockers, carbonic anhydrase inhibitors, Cox-2 inhibitors, fluoroquinolones, gastric acid pump inhibitors, mast cell inhibitors, phenothiazines, prostaglandin antagonists, serotonin receptor agonists, serotonin reuptake inhibitors, sulfonamides and thiazide diuretics. However, many plant or animal products like antibiotics, digoxin, insulin, and the opioid narcotics like morphine and atropine still remain because chemistry has failed to replace them.

No doubt these purified and highly concentrated chemically synthesized medicines showed pronounced effects because of their increased potency, but in most of the cases when used for a long duration and in certain cases when used for acute clinical medications showed drastic side effects. Most of the modern synthetic medicines used to treat some common diseases have been reported to cause a number of undesirable side effects, which sometimes can be lethal. However, the traditional medicines are known to prevent and cure
the diseases with comparatively lesser side effects, provided used watchfully.

Traditional medicines differ from the modern medicines in that the starting point is a history of observation of the effects of plant or animal materials on humans, and it uses crude extracts that are complex mixtures of naturally-occurring compounds, as opposed to single pure compounds of synthetic origin. Now there is increasing evidence that many current chemically synthesized medicines simply suppress symptoms of the diseases and ignore the underlying causes. In contrast traditional medicines, including herbal and glandular products, appear to address the cause of many diseases and yield superior clinical results. As a general rule crude therapeutic products are less toxic than their synthetic counterparts because they contain the total family of medicinal compounds (known and unknown) just as they are found in their natural source and hence offer less risk of side effects. In crude preparations, perhaps, the other components that are present in addition to the active components may be affecting the effects of the active components. These known and unknown components might be acting as synergists for the therapeutic effects and antagonists for the side effects of the active components as well as the other toxic components in the crude preparation. They may be involved in the gastrointestinal absorption and determination of target sites for the active components too. Also it has been reported that most of botanical dietary supplements often contain complex mixtures of phytochemicals that have additive or synergistic interactions. For example, the tea catechins include a group of related compounds with effects that are demonstrable beyond those that are seen with epigallocatechin gallate, the most potent catechin. The metabolism of families of related compounds may be different than the metabolism of purified crystallized compounds7.

Crude extracts vs Active principles

It is generally accepted that the active principles (whether natural or synthesized) may be more toxic than the whole extract or its crude form8. Perhaps other ingredients present in the crude extract modulate the toxicity of the active principle. The best example that can be cited is reserpine, a drug known to have antipsychotic effects, derived from the Indian plant, Rauvolfia serpentina (Hindi—Sarapgandha). Unfortunately, reserpine, when used medicinally, produces adverse side effects (hence not preferred now) than Rauvolfia crude. Researchers in India conducted a placebo-controlled trial in which an Ayurvedic remedy containing R. serpentina in its crude form was tested against the antipsychotic drug Chlorpromazine in the treatment of schizophrenia. The Ayurvedic remedy worked almost as well as the conventional drug but with fewer side effects9.

Other example is of aspirin. In 1500 B. C Hippocrates, a Greek physician, observed that the leaves and bark from Salix alba Linn. (Willow tree) has the ability to relieve fever and pain. Researchers in the last century identified and isolated salicin, a glycoside as active principle. From salicin, salicylic acid and finally aspirin was synthesized. Aspirin is known to cause gastric irritation and hypersensitivity. The plant when used alone does not cause gastric irritation, probably due to the presence of tannins10.

Like a single player in a game cannot be taken as solely responsible for the win, the therapeutic effect of a crude preparation cannot be attributed to the active component(s) only. Rather it is the whole family of biochemical compounds present in it, which interact together to show a particular therapeutic effect. For example St. John’s Wort, Hypericum perforatum Linn. has been reported to show clinical efficacy in mild to moderate depression. It has been observed that neither hypericin nor hyperforin alone presents the antidepressant constituents of H. perforatum, but other compounds like flavonoids and xanthones also contribute to the antidepressant activity10. Benign enlargement of the prostate (BPH) affects nearly 50 per cent of men over the age of 40. Currently, the...
only approved drug for treatment of BPH is marketed under the name Proscar (finasteride); however, extract from the fruits of the, Saw palmetto, *Serenoa repens* (Bartram) Small has actually yielded better results. Numerous studies on this fruit extract at a dosage of 160 mg twice daily have shown it to be effective in nearly 90 per cent of patients within four to six weeks. In contrast, Proscar is effective in reducing the symptoms in only 37 per cent after one year of use 11.

There are so many experimental examples also where the crude plant extracts have shown better therapeutic effects than the purified active components. For example Neem (*Azadirachta indica* A. Juss.), in ancient literature has been documented to cure certain types of tumours. Fujiwara *et al* (1982) have reported that the limonoids and polysaccharides found in the leaves, bark and the seeds show *in vitro* cytotoxic activity against Sarcoma-180 ascite tumour cells13. In another *in vitro* experiment Pettit *et al*15 (1983) investigated a large series of limonoids for *in vitro* activity against the murine P388 lymphocytic leukaemia line13. But as far as the *in vivo* conditions are concerned these components cannot be used because of their acute toxic effects. However, in an *in vivo* study, Balasenthil *et al* (1999) have reported that crude aqueous Neem leaf extract suppresses 7, 12-dimethylbenzanthracine induced oral squamous cell carcinoma of the hamsters by the modulation of drug metabolizing enzymes in the oral mucosa14. Arivazhagan *et al* (2000) have reported the effects of crude Neem leaf extract on hepatic lipid peroxidation and antioxidant status during N-methyl-N’-nitro-N-nitrosoguanidine (MNNG)-induced gastric carcinogenesis in male Wistar rats and concluded that crude Neem leaf extract significantly altered cancer development at extrahepatic sites by influencing hepatic biotransformation enzymes and antioxidants15.

*Momordica charantia* Linn. commonly known as Bitter Gourd or *Karela* is a medicinal plant, used in Ayurveda for treating various diseases including diabetes. Virdi *et al* (2002) have reported that the aqueous extract of powder of fresh unripe whole fruits at a dose of 20mg/kg body wt reduces the fasting blood glucose levels by 48%, an effect comparable to that of Glibenclamide, a known synthetic drug. The extract did not show any signs of nephrotoxicity and hepatotoxicity as evaluated by histological and biochemical parameters, which clearly indicate aqueous extract of the powder of fruit, an edible vegetable, is a safe alternative to reducing blood glucose16.

Sharma *et al* (2001)17 have reported the protective effect of crude, Emblic myrobalan, *Emblica officinalis Gaertn.* (Hindi —*Amla*) extract and its major active component ascorbic acid on the *in vivo* clastogenicity of two chemicals namely Benzo(a)pyrene (a well-known carcinogen) and Cyclophosphamide (an anticancer drug) in mice. The extent of chromosomal aberrations (CAs) and the frequencies of micronucleated polychromatic erythrocytes (MnPCEs) were taken as an index of clastogenicity in their investigation. They observed that the crude extract of *amla* showed a higher protection than its principle component, ascorbic acid. Ascorbic acid alone did not show any significant inhibitory effect on CAs or MnPCEs induced either by Benzo(a)pyrene or Cyclophosphamide. This clearly reflected that the inhibitory effects are related to the total activity of the crude extract, rather than that of a single major component18. In fact, purified form of ascorbic acid has been reported to enhance the clastogenic and carcinogenic effects of some chemicals19. Rossner *et al* (1988) observed ascorbic acid to be ineffective in reducing CAs in...
occupationally exposed workers²⁰. It has been reported that ascorbic acid has a non-significant effect on the antioxidant defense system in mice, whereas the crude amla extract do enhance the reduced glutathione contents as well as the activities of glutathione-S-transferase, glutathione reductase and glutathione peroxidase, suggesting that the antioxidant activity is mainly due to the presence of other compounds present in amla¹⁷,²¹. Ascorbic acid has also been shown to antagonize the toxic effects of certain metallic salts in mammalian systems as well²². However, studies performed with equivalent amount of synthetic ascorbic acid as present in crude fruit extract showed that it was not as effective as the extract in reducing the metal toxicity in mice²⁰,²³.

There can be some examples of the crude preparations with toxic side effects but in those cases the toxicity is not due to drug but due to its adulterant, e.g., toxicity of Tribulus terrestris Linn. (used for urolithiasis and urinary disorders) is often due to Asteracantha longifolia Nees syn. Hydrophilia spinosa T. Anders. mixed with it, which is poisonous⁸. Even in some polyherbal preparations in addition to the active constituents some other components are added to reduce the toxicity or to enhance the therapeutic effect of the active components¹⁰.

**Natural vitamins and hormones vs synthetic counterparts**

**Vitamins**

The synthetic supplements are a combination of some of the separate factors, never the whole complex of synergistic factors found in nature. The best example to understand this fact is of vitamins. It is now believed that the "unknown" co-factors (enzymes, coenzymes, and co-vitamin helpers) found in natural vitamins, not found in synthetic forms, act as catalysts which are indispensable for proper vitamin absorption and maximum utilization, thereby making the natural vitamins more effective. Vitamins in their natural state always exist as living complexes with specific synergistic co-factors, enzymes, phytonutrients and organic mineral-activators, and never as isolated single factor. A vitamin needs all of its synergists to function. Further, there are literally hundreds of such synergists, most of which have not yet been studied but are nevertheless very important. Synthetic vitamins are just the active components of the whole complexes and do not possess these synergistic components. Synthetic vitamins may cause improvement of certain conditions for a short time but the whole complex goes even further.

Research indicates that synthetic vitamins may actually cause nutritional deficiencies. When one takes a synthetic vitamin, it needs the co-factors as found in the natural sources, in order to complete its action. If they are not in the foods one eats, it will draw the co-factors from one’s body. One may feel good for a while but when the co-factors run out, one will begin to feel worse. The prolonged use of synthetics imitates the action of drugs; they over-stimulate rather than feed one’s body. It is very true that when you take a fraction of something it is not as effective as the whole substance. For example ascorbic acid is just a fraction of the biologically utilized Vitamin C complex, which is composed of P-factor, J-factor, K-factor, tyrosinase, ascorbigen complexes and ascorbic acid. The synthetic ascorbic acid is prepared in pharmaceutical industries from corn sugar. It does not contain other components, which the natural vitamin C complex possesses. Because body needs all parts of a vitamin to function, it will leech the other necessary cofactors from itself in order to use the ascorbic acid, which puts a lot of extra stress on the body²¹. A fraction of naturally occurring vitamin is at best a drug not a vitamin, and can only have a drug effect in the body not a physiological or curative benefit.

As far as the synthetic vitamins and nutritional supplements are concerned, the standardization of dose is very difficult. But in the whole-food vitamins and nutritional supplements, standardization is not required because nature believes in the balance, not in potency. So many studies have shown that mega doses of synthetic vitamins can cause negative side effects, which are totally the reverse of normal physiological effects of the natural vitamin complexes. In a case controlled study it was found that men who took 500 mg of synthetic vitamin C daily for 18-month period had a 250% increase in the intima-media lining (inner lining) of the carotid artery. This thickening is an accurate measurement for the progression of atherosclerosis. That is, synthetic vitamin C induced atherosclerosis, even at a 500 mg dose. Whole food Vitamin C protects and repairs the inner lining of blood vessels, and is preventative against atherosclerosis²⁵. It has also been reported that the chemically purified vitamin E (tocopherols) in high unit doses reverses
its effect and produces the same symptoms as a deficiency including bone decalcification\textsuperscript{26}.

Stereoisomerism is another factor, which may be responsible for the differences in the action of the naturally occurring compounds and their synthetic counterparts. For example natural vitamin E (d-\(\alpha\)-tocopherol) is the most biologically active form of vitamin E and is derived from vegetable oil primarily soy bean oil, sun flower oil and corn oil, and contains one isomer, i.e., d-\(\alpha\)-tocopherol. In contrast, synthetic vitamin E (dl-\(\alpha\)-tocopherol) is produced by a chemical reaction of trimethyl hydroquinone with isophytol resulting in a mixture of eight stereoisomers in equal amounts, of which only one (about 12 \% of the synthetic molecules) is identical to natural form of vitamin E.

Researchers have found that natural vitamin E assimilates far better than synthetic versions. Specific binding and transport proteins produced in the liver select the natural d-alpha form of vitamin E and largely ignore all other forms. In one experiment Japanese researchers alternately gave natural and synthetic vitamin E to seven healthy young women. It took 300 mg synthetic vitamin E to equal the blood levels achieved by a 100 mg dose of natural vitamin E\textsuperscript{27}. Researchers at Oregon State University, Corvallis, found that the human body excretes synthetic vitamin E three times faster than the natural form of natural vitamin E\textsuperscript{28}. Also the natural vitamin E is retained in humans at least two times greater than the synthetic form of the supplement\textsuperscript{29}. In an earlier study, researchers found 3½ times higher levels of natural vitamin E in the placental cords of pregnant women than synthetic, after the women took supplements containing both natural and synthetic forms of the vitamin. This is significant because it suggests that the placenta can deliver natural vitamin E to the foetus much more efficiently than synthetic, suggesting that women should take prenatal supplements that contain the natural form of the vitamin\textsuperscript{29}.

**Hormones**

The story of chemically synthesized hormones is similar to that of vitamins. Medroxyprogesterone is an analog, a "look alike", of progesterone. The chemical structure of Medroxyprogesterone closely resembles the chemical structure of naturally formed progesterone in the human body. But, even a slight difference in the molecular configuration of a compound can produce a totally different response from its natural counterpart. Micronized progesterone is transformed by chemical process from the sapogenin, diosgenin, a group of plant steroids, which is found naturally, in yams and soyabeans. Unlike Medroxyprogesterone, micronized progesterone is an exact chemical duplicate of the progesterone that is produced by the human body. Having chemical structure identical to that of the hormone produced in humans, micronized progesterone is essentially non-toxic and has few or no undesirable side effects. It may be more effective than its synthetic counterpart in certain situations such as postmenopausal hormone replacement therapy. Its use in other settings such as osteoporosis prevention and treatment shows promise\textsuperscript{30}. On the other hand, Medroxyprogesterone can lower a patient’s blood level of progesterone. Some women who take Medroxyprogesterone to combat premenstrual syndrome (PMS) or oppose estrogen in menopause report headaches, mood swings and fluid retention. While, women who take natural micronized progesterone often say their mood swings diminish. Women who suffer from migraines as their main complaint with PMS also find that this situation may be corrected by micronized progesterone. In its natural micronized form, progesterone acts as a diuretic, which means the women who take these supplements may have to suffer higher frequency of urination, but they are spared the fluid retention and weight gain experienced by women on synthetic progestin.

**Conclusion**

These days a lot of research is being conducted to see whether this so called advancement in the process of therapy is proper or not. In our view, as far as the research work is concerned, the isolated active components may be helpful in studying the mechanism of action of a medicinal preparation, but for therapeutic purposes the crude preparations are more beneficial. These days more and more peoples are depending upon natural medicines because of their least or no lethal side effects.

It can be concluded that traditional and herbal crude preparations may not be acting like magic bullets of the modern chemically synthesized medicines but these do produce beneficial effects with no or lesser undesirable side effects.
There is a need to reassess the therapeutic properties of the crude traditional therapeutic preparations by scientific methodology, which can lead to their rational use. Collection of scientific data supporting the miraculous medicinal properties of these preparations is also required to take maximum benefits without any fear of undesirable side effects.

References

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**Traditional and Modern Medicinal Chemistry**

Before modern scientific approaches to drug therapy, there was herbal medicine. Relying largely upon trial and error (often fatal error), cures or least preventative therapeutic approaches were chosen from among the rich plant pharmacy. Modern science has unarguably improved upon this approach leading to miraculous chemical cures. Sometimes, however, the process by which herbal medicines were administered has a great impact upon the medicinal effect. Careful attention must be paid to the holders of traditional medicine knowledge when attempting to bring such important discoveries to the modern laboratory. The process/workup/isolation of a product from a “true” herbal cure may yield a vastly different molecule.

The future holds new challenges to disease states and old challenges yet be answered. The marriage of traditional and modern medicinal chemistry will likely be a fruitful and productive adventure (Professor C. M. Thompson, Medicinal Chemistry, Lecture 1; http://www2.umt.edu/medchem/teaching/medchem/mclect1.htm).