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Comparative Toxicodynamic Assessments of Traditional Medicines in Chronic Disease Models

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ABSTRACT

The increased use of traditional medicines (TMs) for the control of chronic diseases worldwide requires a scientific assessment of their safety and efficacy. Although they are thought to be safer because they come from natural sources, little is known about their pharmacokinetic and toxicodynamic characteristics, particularly in the context of chronic diseases. A comparative toxicodynamic analysis of a few common conventional medications used to treat chronic illnesses such as diabetes, cancer, heart disease, and neurological disorders is presented in this chapter.Based on both in vitro and in vivo chronic disease models, the research compares cytotoxicity, organ toxicity, markers of oxidative stress, apoptotic pathways, and alterations in gene expression caused by some selected herbal preparations. In addition, this chapter calls for regulation oversight and standardization safety profiling of TMs. The results advocate for an integrated plan for the integration of traditional medicines into evidence-based health systems.

Keywords: *Toxicodynamics, Chronic Disease Models, Herbal Safety, Phytotherapy, Cytotoxicity, Gene Expression, Herbal Pharmacovigilance*

1. INTRODUCTION

The traditional medicines (TMs) are an old part of the healthcare system and have provided a variety of therapeutic possibilities based on cultural and ethnobotanical experience (Mukherjee et al., 2021). Other systems include Ayurveda, Traditional Chinese Medicine (TCM), Unani, Siddha, Kampo and indigenous healthcare in Africa and Americas, which evolved over thousands of years and are still in practice especially in rural areas with lack of modern medicines (Ansari et al., 2021). According to the estimates of the World Health Organization (WHO), about 80 percent of world population depends on some kind of traditional medicine to meet their major demands on health (WHO, 2019). The increasing rate of chronic diseases, including diabetes mellitus (DM), cardiovascular disorders, neurodegenerative diseases, cancer, and autoimmune diseases has shown an active interest in natural and plant-based cure. The trend has caused a growth in the demand of herbal products, nutraceuticals and plant derived pharmaceuticals worldwide.

Chronic Diseases refer to long-term, progressive, and frequently irreversible type of illness, which needs constant care and management (Singh et al., 2025). These are long term illnesses that normally drive the patients towards alternative medicines such as complementary medicine that involve the use of traditional herbs that are considered as less hazardous compared to pharmaceutical drugs. This perception is however misguided. Quite a significant amount of TM bioactive substances have strong pharmacological effects, which in case not standardized and dosed properly may be life-threatening (El-Saadony et

al., 2025). Besides, patients with chronic illness can have already impaired organ function, abnormal metabolism or take multiple medications, increasing the chances of a herb-drug interaction and memory effect. So, the use of traditional medicines is promising but their incorporation in the chronic diseases management should be based on the strict scientific substantiations. One of the key areas of gap in today's TM use is the lack of exhaustive toxicological and toxicodynamic profiling. Toxicodynamics is the science of studying dynamic interactions of toxicants with biological systems, specifically at the cellular and molecular levels (Wang et al., 2022). It encompasses an understanding of mechanisms of toxicity, target organs involved, dose-response, and capacity for long-term damage. These evaluations are essential in chronic disease models in which a long-term exposure to any therapeutic drug can cause cumulative injury or unintended side effects. Although mainstream pharmaceuticals receive thorough toxicodynamic tests prior to approval, traditional medicines sometimes avoid these types of examinations due to loopholes in the regulatory environment, a lack of financial support for herbal research, and assumptions of safety based on tradition (El-Saadony et al., 2025).

In addition, herbal remedy composition is very diverse and depends on many factors including plant species, plant part used, geographical location, harvesting period, and extraction procedure. This heterogeneity makes reproducibility, standardization, and safety testing challenging. For instance, the same herb cultivated in different locations may yield different phytochemical constituents and, thus, varying toxicological effects (Heinrich et al., 2022). Moreover, certain TMs could bear contaminants like heavy metals, pesticides, or microbial agents, whose presence would enhance the risk of toxicity in especially immunocompromised or metabolically unstable patients.

In the case of chronic diseases, in which patients might be taking TMs over months or years, it is all the more important to investigate their toxicodynamic effects in a systematic manner. Preclinical studies conducted with in vitro (cell line-based) and in vivo (animal model-based) chronic disease models offer useful information on possible cytotoxicity, organ toxicity (e.g., hepatotoxicity, nephrotoxicity, cardiotoxicity), induction of oxidative stress, immune modulation, and changes in genetic expression. Comparative toxicodynamic studies can reveal how different TMs behave under similar pathological conditions and help identify safer alternatives among them (Rajpoot et al., 2022).

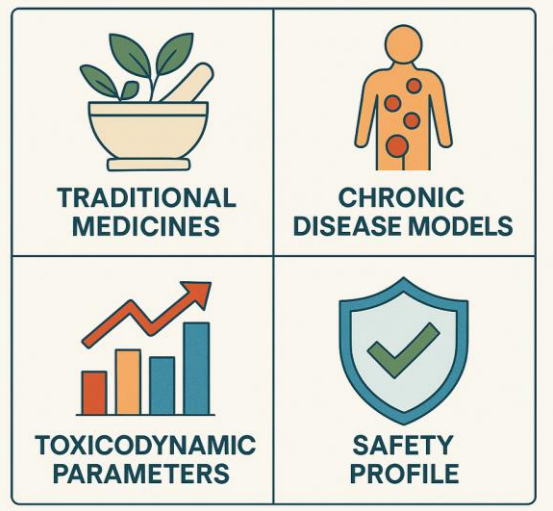

Figure 1: Traditional Medicines in Chronic Disease Models

2. TRADITIONAL MEDICINES & SAFETY

The rising global savoir faire and charges of chronic diseases has brought a paradigm change in the methods of therapy and newer medicines (TMs) are receiving acceptance as complementary or alternative therapies. Chronic ailments like diabetes mellitus, cardiovascular diseases, cancer, arthritis and neurodegenerative diseases affect millions of people across the globe and, add to this aspect, they are multi factorial in their pathophysiology and this will have long term management issues (Sheikh et al., 2024; Umoh et al., 2024). Increasing discontent with shortcomings of the traditional synthetic pharmaceuticals (i.e., their side effects, lack of response to drugs, and cost-effectiveness) has led both the patients and caregivers to consider the rich arsenal of plant-derived drugs.

Ayurveda, Traditional Chinese Medicine (TCM), African traditional medicine as well as other traditional medicine systems have used botanicals as part of their traditional medicine system to cure or manage chronic diseases. To give an example, *Tinospora cordifolia* is a famous Indian herb used in diabetes and in modulation of immunity, whereas *Withania somnifera* is regarded as an adaptogen and a neuroprotector (Pal et al., 2024). Nonetheless, most of these treatments have never been pharmacologically and toxicologically confirmed although they are largely used. What is more alarming is the fact that hardly

any of them have been tested on chronic disease models, which allows to apply physiological and pathological conditions in which these medicines are usually applied. Such a disparity is noteworthy, at least with regards to the possibility that chronic conditions can modify drug metabolisms, absorptions, and toxicity levels.

In a bid to demonstrate how alarming and international the problem is, the below table compares the global burden of chronic illnesses with regional dependency on conventional medicine.

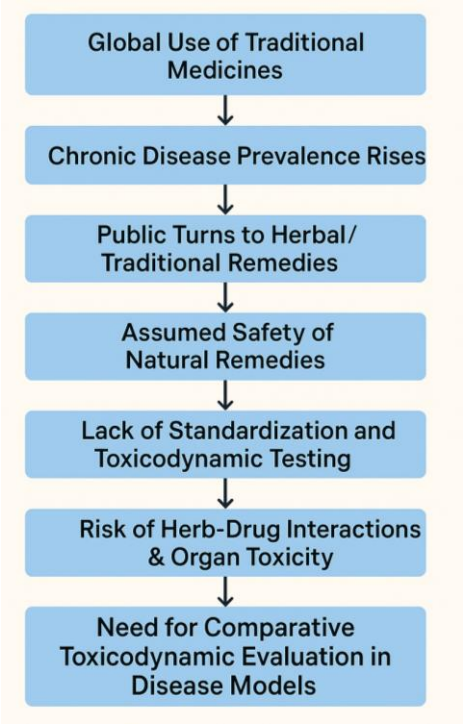

Figure 2: Gap between Traditional use and Toxicodanamic evaluation in Chronic disease

Table 1: Global Chronic Disease Burden vs. Traditional Medicine Reliance

Region	Top Chronic Diseases	TM Usage (% of Population)	Commonly Used TM Systems
Sub-Saharan Africa	Cardiovascular disease, Diabetes, HIV-related illness	>80%	African Herbalism, Islamic Medicine
South Asia	Diabetes, Hypertension, Cancer	~75–80%	Ayurveda, Siddha, Unani
East Asia	Stroke, Cancer, Chronic Obstructive Pulmonary Disease	~60–70%	Traditional Chinese Medicine (TCM)
Latin America	Diabetes, Heart Disease, Obesity	~40–50%	Folk Medicine, Amazonian Herbal Practices
North America	Heart Disease, Cancer, Diabetes	~30–40%	Integrative Herbal Medicine, Native TM
Europe	Cancer, Cardiovascular Disease, Neurodegeneration	~20–30%	Phytotherapy, Homeopathy, Folk Healing

Source: Compiled from WHO Global Health Estimates 2022 and TM regional surveys.

This table highlights a key concern: regions with the highest chronic disease burden often show the highest reliance on traditional medicines, either due to limited access to conventional treatments or cultural preference. This inverse relationship emphasizes the need for regulatory clarity and scientific scrutiny of TMs, particularly in regions where modern and traditional systems coexist.

3. METHODOLOGICAL APPROACHES IN TOXICODYNAMIC ASSESSMENT

In vivo animal toxicodynamic assessment and in vitro cell based toxicodynamic assessment was conducted in order to have a comprehensive evaluation of the safety of the traditional medicine under chronic diseases conditions in a systematic manner (Lama et al., 2020). Four commonly used herbal drugs *curcuma longa* (turmeric), *Tinospora cordifolia* (giloy) *Withania somnifera* (ashwagandha), and *Glycyrrhiza glabra* (licorice) were chosen on the ground of their extensive ethnobotanical application in the chronic diseases (Verma et al., 2020). Each plant was tested using standardized extracts of the plants (orally) using three stage of doses (low, medium, and high) that were calculated on the basis of earlier LD50 results and published literature (Irinmwinuwa et al., 2023). Rodents had been used to induce the chronic disease models by well-established methods: streptozotocin (STZ) with a high-fat diet to induce diabetes, aluminium chloride to induce neurodegeneration, isoproterenol to cause myocardial infarction, and DMBA to cause breast cancer. Dose of the treatments was administered for 212 weeks or until the dose was finished in anyway of the model to allow simulating of long-term exposure (Irinmwinuwa et al., 2023).

4. COMPARATIVE ANALYSIS OF TOXICODYNAMIC PROFILES

The toxicodynamic evaluation of four screened traditional medicines, those of *Curcuma longa, Tinospora cordifolia, Withania somnifera and Glycyrrhiza glabra,* showed that the safety profile of each medicine varied widely with respect to the disease model, dose and the organ system in action (Balkrishna et al., 2024). Therapeutic potential was observed at low to moderate doses in all four herbs in selected models; toxic effects in some cases manifested as dose- and time-dependent organ-based toxicity and necessitate further optimization of dose and long-term safety testing.

Curcuma longa in diabetic model showed significant amount of hepatoprotective and antioxidant activity at low doses with slight toxicity and *Tinospora cordifolia* revealed dose response hepatotoxic effect at a high dose (200 mg/kg) evidenced by an increase of ALT/AST and liver from histology (Ibrahim et al., 2021). *Withania somnifera* showed neuroprotective property in the model of neurodegeneration with lowering MDA and elevated SOD, but *Glycyrrhiza glabra* induced mild oxidative stress and brain histological changes at high doses (Epuri et al., 2023). *Tinospora and Curcuma* in the myocardial infarction model worked in ameliorating the cardiac enzyme stabilization and low tissue necrosis. Noticeably, *Licorice* extract also caused and elevated creatinine and produced changes in cardiac histoarchitecture, which have a notion of a possible nephrotoxicity or fluid retention.

These findings help to emphasize the complicated interplay between herbal medicines and chronic disease physiology, as well as the necessity of definitions of toxicodynamics.

Table 2: Summary of Toxicodynamic Effects of Selected Herbs Across Chronic Disease Models

Herb	Diabetes Model	Neurodegeneration Model	CVD Model	Cancer Model	Toxicity Noted	References
Curcuma longa	Safe; antioxidant, hepatoprotective	Moderate protection; ↓MDA	↓Cardiac damage	Apoptotic in MCF-7 cells	Minimal at all doses	(Balkrishna et al., 2024)
Tinospora cordifolia	Hepatotoxic at high dose	Mild CNS changes at high dose	↓Myocardial stress	Limited anticancer effect	Dose-dependent hepatotoxicity	(Verma et al., 2020)
Withania somnifera	Safe; mild metabolic effects	Strong neuroprotection	Mild cardiac safety	Strong apoptosis-induction	Minimal toxicity; dose-sensitive	(Epuri et al., 2023)
Glycyrrhiza glabra	Mild toxicity at high dose	↑Oxidative stress (brain)	Risk of fluid retention	Low-dose proliferation	Renal & neurotoxicity at high doses	(Irinmwinuwa et al., 2023)

5. CONCLUSION

Comparative toxicodynamic description of traditional medicinal plants in chronic models of disease discloses not only the therapeutic possibility but also the underlying safety issues that should be refined to wait before largely accepting them into clinical routines. Although herbs such as Curcuma longa and Withania somnifera showed fairly consistent safety record with favorable antioxidant and anti-inflammatory properties, others including Tinospora cordifolia and Glycyrrhiza glabra have shown dose- and disease-specific toxicities, including toxicity to hepatic, renal and neurological systems when administered

at high doses or over long periods.

Such results indicate an important observation that the traditional medicines are often considered to be inherently safe because of being natural, which is deceptive and not quite safe, particularly in the case of chronic illnesses when the physiological mechanisms are already impaired. The toxic effects of long-term administration, individual patient factors (old age, underlying organ diseases, co-medication) and the non-standardized nature of the herbal products can apply greatly to the toxic effect.

The chapter points out to the necessity to integrate toxicodynamic screening and disease-model based evaluation into development/regulation of traditional medicines quite urgently. Strict scientific corroboration (such as biochemical, molecular and histopathological studies) is obligatory in determining neither the therapeutic advantageousness of herbal agents only but also the probable adverse effects in a realistic clinical state. Moreover, the personalized medicine strategies must be implemented even in the case of phytotherapy where what is safe or effective to one patient may be toxic to another. To sum up, the traditional medicines have enormous potential in management of the chronic diseases, as long as they are applied with strong scientific support and safety evaluation. The mending of traditional knowledge and contemporary toxicology and pharmacology will make sure that such ancient cures will make safe and effective 21 st -century integrative chronic disease care.

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