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MECHANISMS AND EFFECTS OF CHRONIC TOXICITY IN HUMANS WITH SPECIAL REFERENCE TO DUSHIVISHA: A COMPREHENSIVE REVIEW

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ABSTRACT

Background: Chronic toxicity is an emerging public health concern marked by the gradual accumulation of low-level toxic substances within human tissues leading to progressive multisystem dysfunction. While modern toxicology effectively identifies individual toxins and acute mechanisms, it often struggles to address the cumulative and synergistic effects of long-term, low-dose exposure. The Ayurvedic concept of Dushivisha which is defined as a partially neutralized toxin that persists in the body, offers a complementary, systems-based framework for understanding chronic toxicity.

Objective: To explore and analyze the concept of Dushivisha from Ayurveda in the context of chronic toxicity and to correlate its classical descriptions with contemporary toxicological mechanisms such as oxidative stress, bioaccumulation, enzyme inhibition and mitochondrial dysfunction. The study further aims to evaluate the relevance of an integrative approach combining Ayurvedic detoxification principles with modern medical perspectives for a more comprehensive understanding and management of chronic low-dose toxic exposure.

Methods: A systematic literature review has been undertaken utilizing multiple academic databases including PubMed, Google Scholar, Science direct , classical ayurvedic texts (eg.Charak Samhita, Sushrut Samhita) and Ayurveda focused repositories such as Ayush Research Portal.

Result: Dushivisha represents a chronic, low-grade toxic state distinct from acute poisoning, where accumulated toxins weaken digestion (Agni) and generate Ama, promoting inflammation. Long-term exposure to toxins causes oxidative stress and multi-organ damage. It leads to tissue dysfunction, channel blockage and chronic conditions, paralleling modern toxins like pollutants, chemicals and heavy metals.

Discussion: The Ayurvedic concept of Dushivisha explains chronic toxicity by addressing cumulative, low-dose exposures often overlooked in modern toxicology. It correlates with bioaccumulation and systemic dysfunction seen in chronic diseases. Ayurvedic therapies, including detoxification and

rejuvenation, along with formulations like Dushivishari Agada, offer a holistic approach for managing long-term toxic effects.

Conclusion: The concept of Dushivisha remains highly relevant today in explaining chronic toxicity and lifestyle diseases. Gradual toxin accumulation can disrupt multiple body systems over time. Combining Ayurvedic insights with modern science supports better understanding and management. Preventive care, detoxification and rejuvenation therapies offer practical strategies while further research can strengthen integrative public health approaches.

Keywords: Chronic toxicity, Dushivisha, Bioaccumulation, Oxidative stress, Heavy metals, Ayurveda, Detoxification, Chronic disease, Environmental toxins, Systems-based toxicology

INTRODUCTION

Chronic toxicity has become a defining health issue of the 21st century. The World Health Organization reports that exposure to environmental toxins is responsible for an estimated 12.6 million deaths each year. Prolonged low-level exposure plays a significant role in the global burden of disease, contributing to the development of cardiovascular conditions, cancers, neurological disorders and metabolic dysfunctions [1].

Unlike acute poisoning, which presents rapidly, chronic toxicity develops gradually and often remains undetected until significant damage has occurred. Human exposure to multiple toxicants occurs through diverse pathways like inhalation of contaminated air and dust particles, ingestion of contaminated water and food and dermal absorption of chemicals from consumer products. The toxicity of these substances depends on their chemical properties, dose and route of exposure, duration of exposure and the extent of bioaccumulation within tissues. Environmental contamination now includes:- Heavy metals (mercury, lead, arsenic, cadmium), microplastics, pesticides, industrial chemicals, pharmaceutical residues and endocrine disrupting compounds etc. These substances persist in ecosystems and bioaccumulate, contributing to long-term disease risk.

Introduction to Dushivisha as a Conceptual Framework

Dushivisha refers to toxins that have been partially neutralized but remain harmful when retained in the body over time. Classical Ayurvedic texts describe these toxins as dormant substances embedded in tissues that become active under certain conditions. It denotes any toxic agents derived from sthaavar, jaangam or kritirma visha that have undergone partial detoxification whether through therapeutic interventions, environmental influences or endogenous physiological defences, yet continue to retain residual toxicity and the potential to exert chronic effects [2].

Rationale for Integrative Approach

Modern toxicology provides detailed molecular mechanisms, quantifiable dose-response analysis and evidence based identification of individual toxins, whereas Ayurveda contributes holistic system based understanding, individual susceptibility based on constitutional factors (Prakriti), detoxification and rejuvenation strategies validated through centuries of clinical application. Combining both approaches provides a more complete framework for managing chronic toxicity based understanding.[3]

Key Mechanisms of Chronic Toxicity

1. Reactive Oxygen Species (ROS) generation and oxidative stress

Reactive oxygen species (ROS) production and the resulting oxidative stress are widely recognized as common underlying mechanisms in most chronic toxicant exposures. Heavy metals such as mercury, lead, arsenic and cadmium impaire cellular antioxidant defence systems by interacting with intracellular glutathione (GSH) and sulfhydryl (-SH) groups present in key antioxidant enzymes such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx) and glutathione reductase (GR) [3]. This interaction leads to the inhibition or inactivation of these enzymes which results in the weakening of the

cell's antioxidant capacity. As a consequence, ROS accumulate within cells leading to oxidative damage of essential biomolecules such as lipids, proteins, and DNA.

2. Bioaccumulation

Bioaccumulation occurs when organism absorbs a toxic substance at the rate greater than its elimination . Thus, toxic substances whose biological half life remains long, becomes the greater risk of chronic poisoning [4]. The bioaccumulation of toxic substances in specific tissues plays an important role in causing damage to particular organs. Some toxins tend to collect in certain parts of the body which determines where their harmful effects appear. For example, mercury accumulates in the brain and affects the nervous system, cadmium collects in the kidneys and causes kidney damage and lead is stored in bones, where it can remain for a long time and continue to affect the body[5]. Microplastics demonstrate particular tendency for accumulation in the kidneys which indicate major target organ susceptibility [6] .

3. Cellular dysfunction

Chronic exposure to toxicants leads to cellular dysfunction through a various interconnected mechanisms. These agents interfere with fundamental cellular processes such as growth, proliferation, differentiation and tissue repair. At the molecular level, selective toxicity often arises from specific interactions between metals and biological macromolecules. For example Lead (Pb) inhibits heme biosynthesis by targeting key enzymes such as aminolevulinic acid dehydratase and ferrochelatase whereas Cadmium (Cd) disrupts mitochondrial apoptotic pathways through its effects on Bcl-2 family proteins.[7]

Similarly, microplastics exert complex toxic effects for example induction of oxidative stress, inflammation, apoptosis and genotoxicity. Emerging evidence suggests that their mechanisms of action involve pathways such as ferroptosis in renal tissues and fibrosis induced by transforming growth factor beta 1 (TGF-β1), which shows their potential to disrupt cellular homeostasis.[8]

4. Chronic Inflammation

Chronic toxicant exposure leads to the activation of inflammatory signaling pathways. Such exposures stimulate the production of pro-inflammatory cytokines, promote immune cell recruitment and sustain a state of chronic systemic inflammation. In the context of air pollution, these effects are mediated through multiple biological pathways which contribute to the onset and progression of cardiopulmonary diseases and increasing the risk of mortality[9].

5. Endocrine disrupting chemicals

Endocrine disruption represents a key mechanism underlying the chronic toxicity of many environmental contaminants. A group of substances known as endocrine-disrupting chemicals (EDCs) can imitate or interfere with normal hormonal signalling pathways. These compounds, including pesticides such as DDT and industrial chemicals like Bisphenol A (BPA), have the potential to disturb reproductive function, thyroid regulation and metabolic homeostasis. Prolonged exposure to EDCs has been linked to adverse health outcomes including developmental defects, reduced fertility and an increased risk of hormone-related cancers is another significant mechanism of chronic toxicity [10].

6. Epigenetic factors

Epigenetic factors involve changes in gene expression without modifying the underlying DNA sequence. These factors induces alterations in DNA methylation , histone modifications and non-coding RNA expression . These changes may be long lasting and in some cases transgenerational. By altering gene regulation, epigenetic modifications can affect disease susceptibility and play a significant role in the long-term health consequences of sustained toxic exposure [11].

Systemic Effects of Chronic toxicity

1.Hepatotoxicity

A wide range of environmental contaminants can adversely affect hepatic tissue through multiple and interrelated mechanisms that collectively hampers liver function. For example :- PMMA-derived microplastics have been shown to induce liver injury by promoting inflammation, generating oxidative stress and disrupting lipid metabolic pathways [12]. Similarly, aflatoxin B1, a potent mycotoxin, mediates hepatotoxic effects through mechanisms involving oxidative stress, mitochondrial dysfunction and activation of apoptotic signaling pathways [13]. In addition, chronic exposure to phthalates also interferes with hepatic homeostasis by impairing gap junctional intercellular communication and activating MAPK/Erk1/2 signaling pathways, further contributing to liver dysfunction [14].

2.Nephrotoxicity

Kidneys are highly susceptible to environmental toxins. Exposure to contaminants such as arsenic and fluoride has been shown to disrupt renal ultrastructure, suppress antioxidant enzyme activity and elevate markers of oxidative stress [15]. Likewise, prolonged exposure to polystyrene-based microplastics contributes to renal fibrosis through ferroptosis-related pathways. Evidence indicate that inhibition of ferroptosis can mitigate epithelial cell death and reduce fibroblast activation [16]. In addition, perfluorooctane sulfonate (PFOS) induces renal toxicity by promoting oxidative stress and interfering with essential physiological processes within the kidney [17].

3.Neurotoxicity

Chronic exposure to environmental toxicants cause neurotoxicity and neurodegenerative changes. For example:- mercury disrupts brain function by increasing oxidative stress and altering monoamine oxidase activity, which affects key neurotransmitter systems such as dopamine and serotonin [18]. Persistent systemic inflammation also contributes to neurotoxicity by disturbing tryptophan metabolism and increasing the production of neurotoxic kynurenine which is associated to aging, frailty, elevated inflammatory markers (e.g., TNF-αR1 and IL-6) and reduced motor performance [19]. Formaldehyde produces chronic toxicity which affects the brain, upper respiratory tract, lung, bone marrow and various cell cultures through inflammation, oxidative stress and genotoxicity [20].

4.Cardiovascular effects

Chronic exposure to environmental toxicants shows hazardous effects on the cardiovascular system. Chronic mercury exposure is associated with an increased risk of cardiovascular complications such as myocardial infarction, cardiac arrhythmias and dysfunction of the autonomic nervous system [21]. Fine particulate matter (PM2.5) has been strongly linked to adverse cardiovascular outcomes such as myocardial ischemia, infarction, heart failure, arrhythmias and stroke along with elevated mortality risk. These effects are largely mediated through mechanisms involving systemic inflammation, oxidative stress and disruption of autonomic regulation [22]. Similarly, arsenic exposure contributes to the development of hypertension and atherosclerosis, primarily through reactive oxygen species (ROS)-induced oxidative damage and impairment of vascular function [23]

5.Carcinogenicity and genotoxic effects

These represent critical chronic toxicity outcomes. Arsenic, cadmium, chromium and nickel are classified as Group I carcinogens with chronic exposure producing skin, lung, urinary bladder and liver cancers through multiple mechanisms including oxidative DNA adduct formation, altered DNA methylation and genomic instability [24]. Similarly Ochratoxin A causes nephrotoxicity, carcinogenicity and teratogenicity through combined indirect mechanisms of genotoxicity, oxidative stress and epigenetic factors [25].

6.Reproductive effects

Long-term exposure to toxic substances can significantly affect reproductive and developmental health. For example microplastics can harm male fertility by disrupting sperm production, reducing sperm count, motility and viability and causing damage to testicular cells. In females, prolonged exposure may interfere with the estrous cycle, impair follicle development, reduce the number and size of oocytes and lead to inflamed ovaries and a lower ovarian reserve [26]. Phthalates such as DEHP (di-2-ethylhexyl phthalate) act as endocrine disruptors. They can promote the growth of breast cancer cells through progesterone receptor dysregulation and are also associated with infertility, early puberty and obesity[27]. Similarly, chronic radiation exposure across generations has been shown to reduce offspring production by 40%, worsen sperm quality, disrupt normal cell cycles and trigger increased stress-response activity at the genetic level [28].

Dushivisha - Mechanism and Manifestations

Classical Ayurvedic texts like Charaka Samhita and Susruta samhita describes Dushivisha as a mild form of Visha that does not kill immediately but becomes active later especially when agni is weak or the body is exposed to aggravating factors.

दूषितंदेशकालान्नदिवास्वप्नैरभीक्ष्णशः ।

यस्माद्दूषयते धातून तस्माद्दूषीविषं स्मृतम् ॥

च.चि.२३/३१

It may originate from Sthavara, Jangama or Kritrima Visha. Because of mild potency and Kapha aavran, it stays dormant, producing symptoms only under favorable aggravating conditions such as consumption of incompatible food (Viruddhahara), seasonal changes (Kala) or suppressed natural urges.

Continuous exposure to low grade toxins from diet, lifestyle and environment causes agnimandya. Weak agni is unable to digest food properly and does not burn toxins which leads to the formation of Ama (metabolic toxins). Ama gets absorbed in the Ras dhatu and circulates throughout the body. Ama interacts with doshas and dhatus which disturbs their normal function and vitiates them. Vitiated doshas along with Ama obstruct the micro and macro channels causing srotodushti which impairs the transport of nutrients, oxygen and elimination of waste. Nutrients do not reach properly and waste does not eliminate, leading to degeneration and dysfunction of body tissues (Dhatus).Consequently all seven dhatus get vitiated resulting in their qualitative and quantitative impairement. Chronic toxic load and dhatu dushti results in depletion of Ojas which is the root of vitality, immunity, strength and mental well being. Oja kshay results in weak immunity and poor resistance against pathogens and stressors, thus body becomes susceptible to infections and various diseases like skin disorders, metabolic disorders, liver disorders, autoimmune disorders, cardiovascular disorders, respiratory disorders, neurological and psychological disorders etc.

In this way dosha, dhathu, mala samyata has been impaired leading to acute disturbances. These acute conditions tend to become sub-acute and chronic and continue as such. Thus, they retained in the body, impeding the restoration of normal equilibrium of the doshas, dhatus and malas leading to various functional and organic disturbances.

Clinical Features of Dushivisha

The prodromal manifestations of Dushivisha include excessive drowsiness, a sensation of heaviness in the body, frequent yawning, looseness of joints, piloerection (horripilation) and generalized body aches [29]. As the condition progresses, affected individuals may develop diarrhea, altered skin complexion, foul breath, impairment of the senses of smell and taste and persistent excessive thirst. Additional clinical features include slurred or incoherent speech, recurrent vomiting, psychological distress or sadnes and episodic loss of consciousness. Features resembling Dooshyodara (abdominal pathology associated with chronic toxic accumulation) may also be observed [30].

Subsequently, patients may experience a feeling of intoxication after food intake, impaired digestion, loss of appetite, erythematous skin eruptions, edema of the face and extremities, urticarial rashes, syncope, ascites, vomiting, diarrhea, abnormal discoloration of the body, convulsive or epileptic episodes, intermittent fever and worsening thirst [31].

Complications of Dushivisha

Chronic persistence of Dushivisha may lead to the development of various systemic complications. These include fever (Jwara), burning sensation (Daha), hiccups (Hikka), abdominal distension (Adhmana), infertility (Vandhyatva), edema (Shotha), diarrhea (Atisara), loss of consciousness (Murcha), cardiac disorders (Hṛidroga), psychiatric manifestations (Unmada) and tremors (Kampa) [32]. Similar complications involving different organ systems may also occur depending on the nature and duration of toxic exposure.

These manifestations indicate the progressive and multisystemic effects of retained toxins on physiological functions. Therefore, management should not only focus on eliminating the underlying toxic state but also include condition-specific therapeutic interventions aimed at addressing the individual complications according to their clinical presentation.

Modern Mechanisms and Ayurvedic Framework Concordance

From the perspective of modern physiology, various substances in the body such as enzymes, hormones, catalysts, etc., undergo transformations and transmutations. When these substances fail to function properly or completely, they result in the formation of different auto reactive metabolites that the body cannot utilize. Further, these metabolites accumulate in different systems, disrupting the normal functioning of the respective systems. In this context, these accumulated metabolites may be considered akin to the concept of Ama in Ayurved.

In today's era, the people working in industries like enamel workers, glass blowers and printing workers often exhibit typical symptoms of chronic lead poisoning such as constipation, tremors and menstrual disarrangements. Due to continuous exposure, lead gradually accumulates in the body and produces toxic effects resembling Dushi Visha. Similarly, chronic occupational poisoning of arsenic, copper and mercury has been observed in workers handling these substances due to prolonged exposure in the respective industries.[33] Farmers are also at high risk due to regular exposure to organophosphorus pesticides, organochlorine pesticides, weed killers like parquet, chlorophenyl acetates and chlorates which are sprayed to prevent infection in plants. Daily exposure to such chemicals often results in symptoms such as dysphasia, oropharyngeal ulcers, coughing and pain in the abdomen which closely resemble symptoms of Dushi Visha[34].

Modern Mechanism (Toxicology)	Ayurvedic Concept	Point of Concordance
1. Oxidative stress (ROS generation, inhibition of antioxidant enzymes)	Impaired Agni and Ama formation	Both describe metabolic dysfunction where improper digestion/metabolism leads to accumulation of toxic intermediates (Ama) similar to oxidative damage.
2. Bioaccumulation of toxicants in tissues	Dushivisha localization	In modern science gradual accumulation of toxins in different tissues corresponds to Dushivisha
3. Multi-organ involvement	Srotorodha ,Dosha vitiation and Dhatu kshay	Toxic effects across multiple organs align with obstruction of body channels (Srotas) , widespread imbalance of Doshas and Dhatu kshay
4. Weakened immunity	Ojo kshay	Oja kshay results in weak immunity and poor resistance against pathogens and stressors
5. Genetic polymorphism affecting detoxification	Prakriti (individual constitution)	Individual variability in susceptibility to toxins corresponds to Prakriti which determines how a person responds to toxic exposure.
6. Delayed toxicity / latency period	Dormant state of Dushivisha	Latent period between exposure and disease manifestation matches the concept of Dushivisha remaining inactive until triggered.

Treatment Modalities

Cumulative toxicity caused by *Dushivisha* has its own targeted treatment approach which provides benefits beyond just managing symptoms. Ayurveda emphasizes addressing the root cause by following protocols like:-

1. Nidaan Parivarjan :- Removal from the source of exposure.
2. Detoxification (Shodhana):- Ayurveda places strong emphasis on Shodhana (body purification) as the foundation for preventing toxin accumulation. It involves therapeutic procedures that help remove toxins from the body based on doṣha involvement through :-

(a) Vamana (Therapeutic Emesis):- Used when toxins are mainly present in the upper digestive tract, especially in Kapha-dominant conditions. It helps expel accumulated mucus and toxins.
(b) Virechana (Therapeutic Purgation):- Helps eliminate toxins from the lower gastrointestinal tract, particularly useful in Pitta-dominant disorders. It supports liver and intestinal cleansing.
(c) Basti (Medicated Enema):- Highly effective for Vata-related conditions. It cleanses the colon and helps remove deeply seated toxins from the body.
(d) Raktmokshan (Bloodletting) :- Used to eliminate vitiated blood through Siravyadh, Jaloukavacharan, Shringa, Alabu and Prachhann.

3.Sanshaman Chikitsa :- Internal use of agad yogas such as Dushivishari Agad, Pippalyadi Agada, Amrit sarpi etc. contain ingredients with documented anti-inflammatory, hepatoprotective and blood-purifying properties. These formulations show potential in managing chronic toxicities associated with cosmetics, contaminated food and environmental pollution [35].

4. Rejuvenation (Rasayana) Therapy:- After detoxification, Rasayana therapy is used to rebuild and strengthen the body. It helps restore tissue health, improve metabolism and enhance the body's natural defence mechanisms. Common herbs used include Ashwagandha ,Guduchi, Neem ,Haridra, Amalaki, Tulsi etc. These herbs act as antioxidants and immune boosters, helping the body recover from toxin-related damage [36].

5. Diet and Lifestyle Modifications:- Ayurveda strongly focuses on preventing toxin formation by maintaining proper diet and daily habits by:-

[a]Avoiding Viruddha Ahara (Incompatible Foods)

[b] Eating the right food combinations prevents the formation of Ama (toxins).

[c] Regular Panchakarma:- Periodic detox therapies help maintain internal balance and prevent toxin buildup.

[d] Healthy Daily Practices like oil pulling, tongue scraping and drinking herbal teas support digestion and help in natural detoxification.

DISCUSSION - Toxic substances cause disease through a combination of general cellular damage mechanisms and organ specific effects. Common pathways such as oxidative stress, inflammatory signalling and genetic damage occur across many cell types, but clinical outcomes depend on where the toxicant accumulates, along with factors like genetic susceptibility, nutritional status and immune function. Variations in genetic polymorphisms influence the activity of xenobiotic metabolizing enzymes, antioxidant defence systems and DNA repair mechanisms, thereby affecting an individual's ability to efficiently eliminate or retain toxic substances. When multiple processes including mitochondrial dysfunction and inflammatory activation act together, they can exceed the tissue's ability to repair itself which leads to more severe diseases in individuals with multiple exposures.

In Ayurveda the concept of Dushivisha links underlying molecular disturbances with clinical manifestations through Dosha imbalance and Dhatu dysfunction. Involvement of Rakta Dhatu (blood tissue) often presents as skin disorders, serving as visible indicators of internal pathology. Additionally, Srotorodha (channel obstruction) explains how the accumulation of toxins disrupts nutrient transport and waste elimination ultimately impairing normal tissue function [37].

Ayurvedic therapies such as Shodhana (detoxification), Shamana (symptom management) and Rasayana (rejuvenation) exhibit multiple biological activities like anti-inflammatory, antioxidant, antimicrobial, hepatoprotective and immunomodulatory effects similar to multi-target therapeutic approaches. The clinical effectiveness of Agad yog such as Dushivishari Agada, Pippalyadi Agada etc. in managing chronic toxicity from dietary, environmental and cosmetic sources highlights the practical relevance of the Dushivisha concept.

CONCLUSION

Cumulative toxicity is a complex, multifactorial health issue driven by continuous exposure to environmental and dietary toxins. It operates through mechanisms such as oxidative stress, inflammation and bioaccumulation ultimately leading to systemic diseases. The Ayurvedic concept of Dushivisha provides a valuable systems based perspective that complements modern toxicology. Integrating both approaches offers a more comprehensive understanding and opens pathways for more effective prevention and treatment strategies. Future healthcare models should embrace this integrative framework to better address the growing burden of chronic toxicity in modern era.

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