Review Article

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NEW OUTLOOK ON CONCEPT OF AMA: FREE RADICALS OR XENOBIOTICS

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ABSTRACT

Ama (incomplete chyme, residual juice of indigested food) is a remnant of incomplete, improper digestion and metabolism without attaining proper finality. Ama makes an avastha (stage) where the component Ama in association with doshya dushayadi results in acute or chronic ailments. The peculiar and unique quality of Ama is to turn asamyukta (inassimilable) a tough bond with normal body elements. Because of this tough association, the dissociation and excretion becomes impossible. This quality of is compared with toxic manifestation of xenobiotics which are non excretable. If has to be made excretable, then it has to be converted from non excretable form in to excretable form. Or if it has to be made excretable, then it has to be converted into nontoxic or less toxic water soluble element. This is also similar to that of conversion of samadosha dhatu mala into niramaavastha where it is totally detoxified and its excretion is possible. The present article aims at a clear faceoff with concept of xenobiotics and concept of Ama which facilitates better understanding or paves way for a perfect management of the disease associated with Ama.

In this process of biotransformation the way which is more actively involved with the phase I, namely Z*ingiber officinale*, phase –II Z*ingiber officinale* and *Allium sativum* and phase-III *Allium sativum* and *Cassia senna*. These are explained with an intention of attempting the implementation of newly introduced concept as mentioned above.

Keywords: Ama, free radicals, Biotransformation, xenobiotics, herbal drugs

INTRODUCTION

The concept of Ama in Ayurveda is a deep rooted one. Needs to careful and close consideration as all diseases have their beginning with Ama,In any deviation from its normal function of Agni there is a product called Ama.Ama is as important as dosha is causing a disease; hence it is said as Sarvadosha Prakopanam (triggers all the humours). This itself shows the potentiality of Ama. Its role in certain disease entities is as significant as that of dosha. Ex: Amavata, Vishuchika. Hence it had been termed as "Amadosha" (Humour associated with Ama) in these contexts. Similarly because of its rapidity and toxic like action on the human system i.e "Ashukariswabhava" (Acute onset) it has been described as Amavishain other instances.

Biophysical Properties of Ama

In Sarvanagasundara, (a commentary on Astanaga Hridaya) it is said that ama is liquid, heavy, different colors, slimy, viscid, thread, sticky, yields foul smell, increased sourness, thick turbid and obstructing various pathways etc[1]. (Figure 1)

Probable understanding in Allied Sciences

In the allied sciences the Ama is considered to be the toxin which needs to be expelled out from the body.[2]

Ama if continues in the state of asamyukta (improperly for longer period without elimination), it attains shuktata in which the generation of Amagunaorvishaguna that is toxic condition takes place and becomes endangered to life is called as Amavisha condition.

So, at the level of Amavisha (Ama in toxic form) Amaswaroopa or gunas are similar to that of vishaguna. The color of Ama as described by Vagbhataas various colors depending upon variance in tissue and process involved and hence termed anekavarna (different colors)[3]. (Figure 2)

Free Radicals and its resemblance with Ama

Free radical is an atom/molecule that contains one or more unpaired electron, which requires neutralization by free radical scavengers. Thus it exists in an incomplete metabolic state which is also the state of Ama described as Avipakvam (incompletely digested/metabolized). Next it is seen that when produced, free radicals are inassimilable to body produced, free radicals are inassimilable to body components and exist in Free State. Similar is the case with Amawhen it is produced it

remains in inassimilable state and hence termed asamyuktam (improperly mixed).

Ama dosha is a condition in which tridoshas, seven dhatus, as well as three malas (toxic products) become permeated with ama produced in the amashaya (stomach) and this ama dosha leads to the production of diseases[5].

Free radicals cause damage to cell membrane and thus the cell is destroyed. This destruction may lead to purification and foul smell generation, which is similar to one of the property of Ama described as durgandham (bad odor).

Though Ama remains in the body as asamyuktam (inassimilable), but due to its properties like bahupicchilam (excessively sticky) etc. It sticks to normal healthy body tissues very quickly; similar is the case with free radical. To seek stability in their structure they quickly attack the healthy molecules of the body and thus setting a chain reaction. The cells throughout the body are continuously exposed to these damaging molecules and the same has been described for Ama as sadanamsarvagatranam (Ama causing general malaise).

Contradictory aspects of Ama and Free Radicals

Xenobiotic is the broader term which includes various forms of toxins that are rarely eliminated from the body unchanged. Free radicals are one of the variety of xenobiotic caused due to highly reacting electrophilic metabolites (atyagni/intensified digestive fire) and it is always intense with reference to inducing cytotoxic, teratogenic, Autogenic or carcinogenic effect (Ama visha).

Ama constitutes Ama rasa, Ama dosha and Amavisha. Free radical is a form of Amavisha. There are certain xenobiotics which may not be lethal where it may be subclinical waiting for next outbreak (leenadosha/deep hidden humour) .Thus free radical is a part of xenobiotics and Ama can be everything related to xenobiotics with its various levels.

Introduction to the concept of Biotransformation

Biotransformation is a process whereby a substance is changed from one chemical to another by a chemical reaction within the body. It is vital for survival and also acts as an important defense mechanism.Occasionally it produces unusually reactive metabolites reacts with cellular macromolecules.Most of the chemical reactions occur only because of enzymes. Without enzymes slowness or absence of biotransformation occurs and that leads to health problems. Most of the enzymes have specificity, “lock and key” relationship. Biotransforming enzymes are available in normal amount and in some situations can be used up at a rate that exceeds the body’s ability to replenish them. Biotransforming enzymes are widely distributed throughout the body, primarily the liver. Kidneys and lungs are next to liver. It includes Phase I and Phase II reactions[6].

Introduction to the concept of Xenobiotic

A xenobiotic is a foreign chemical substance found within an organism that is not normally or naturally produced by or expected to be present within that organism. It can also cover substances which are present in much higher concentration that are usual. Specifically drug such as antibiotics are xenobiotics in humans as humans do not produce themselves nor are part of normal diet[7].

Natural compounds can also become xenobiotics if they are taken up by another organism such as the uptake of natural human hormones by fish downstream of sewage treatment plant outfalls or the chemical defenses produced by some organisms as protection against predators.

Xenobiotics and Ama

- A Xenobiotic is a compound foreign for the organism. It may be of natural origin or it may be produced by Human[8].
- Xenobiotics are rarely eliminated from the body unchanged. Majority of them undergo conversion in the body in various extents.
- Xenobiotic needs highly efficient mechanism for detoxification and elimination from the body[9].

Biotransformation or Detoxification

- It refers to series of biochemical reactions occurring in the body to convert the foreign (often toxic) compounds to non toxic or less toxic and more easily excretableforms.
- Man is continuously exposed to several foreign compounds such as drugs, pollutants, food activities, cosmetics, pesticides, unwanted compounds produced in largeintestine by bacteria, waste materials produced in normal metabolism which are toxic and hence to be eliminated quickly from the body[10].

Biotransformation of Xenobiotic takes place mainly in Liver which is equipped with enzyme machinery, Kidney and other organs. (Figure 3)

Role of Liver in Biotransformation

- Biotransformation reactions normally result in detoxification. Some chemicals may also be enzymatically converted into highly reacting electrophilic metabolites (epoxides, free radicals etc) which may induce cytotoxic, teratogenic, mutagenic or carcinogenic effect through reactions with various cellular constituents.
- The initial biotransformation is of less toxic chemical to one or more reactive metabolites by a process commonlyreferred as metabolic activation which is essential step for many chemical induced toxicities[11].
- Thus in the process the steps that undergo are

i. Oxidation
ii. Reduction
iii. Hydrolysis
iv. Conjugation

Oxidation

Large numbers of foreign molecules are detoxified by oxidation [12]. Eg: Alcohol, aldehydes, amines, aromatic hydrocarbons and Sulphur compounds.

Oxidation is the major process of detoxification involving the microsomal enzyme cytochrome P450 which is an inducible, NADPH dependent hemoprotien.

Oxidation can be enhanced by Agni Deepana as it is lead by enzymatic action where these enzymes are nothing but dhatwagni (tissue enzymes). (Figure 4)

Hydrolysis as Pachana (Digestion) and Doshapaka (digestion of humours)

It is water separation and cleavage of chemical bonds by addition of water.

- Aspirin Salicylic acid + Acetic acid
- Atropine Tropic acid + Tropinein liver

Excreted in Urine and Feces

Conjugation – Achieved after Snehana (Oleation) and Swedana (Sudation)

- It is the process in which foreign compound combines with a substance produced in the body.
- The turning of substance into hydrophilic (water soluble) state in the body (Figure 5)

There are two basic groups of Xenobiotics according to their chemical feature or polarity;

Polar (Hydrophilic)

Xenobiotics are well soluble in water. They get through membranes poorly. They must use channels and transporters in the blood stream. They are transported freely and are rapidly eliminated in urine. They do not need transport protein.

Non polar (Lipophilic, Hydrophobic)

Xenobiotics that are water insoluble or poorly soluble in samaavastha which is avila (gel like consistency), tantula (thread like), piccila (greasy) and abhishyanda (oozing**).** They may get stuck in membrane (Sanga by Ama due to srotorodha). In blood stream transport of protein is needed andthus they are slowly eliminated. Since bound to protein they cannot reach the urine as glomerular membrane does not allow protein. Aim of lipophilic xenobiotics metabolism is to change their molecule to hydrophilic molecule to make elimination easier. Samaavastha (associated with ama) to Niramaavastha (dissociated from ama) and then subjected to shodhana (purification therapy). During this process the consequences of metabolism includes oxygen defects (hypoxia in liver), tissue damage, impairment of other metabolic process, interaction between metabolic by products and other cell components resulting in formation of more harmful compounds (Ama visha).

- Thus natural and spontaneous metabolism of Ama in liver may not be sufficient to eliminate.This biotransformation capacity can be enhanced, unchanged and unmetabolisable materials can be made eliminated only with intervention by Ayurvedic therapeutic procedure [14]
- Agni deepana (intensifying the digestive fire) enhances the enzymatic action required for Oxidation
- Pachana (Digestive) enhances the Reduction and Hydrolysis
- The lipophilic compound can be converted into hydrophilic component (conjugation) by Snehana (oleation) and Swedana (Sudation).
- The elimination of Xenobiotics (Ama) finally happens after successful Vamana (emesis), Virechana (purgation), Nasya (Nasal errhinics), Raktamokshana (Bloodletting)

Herbal drugs that act on Xenobiotics

Food and medicinal herbal compounds possessing relevant antioxidant properties are xenobiotics for the human being. The Gluthathione -S-tranferases (GST) is a group of enzymes which are known as cellular detoxification enzymes. There is a high correlation between induction of these enzymes and inhibition of carcinogenesis. The GST group of enzymes playsamajor role in the detoxification pathway and help in the conversion of reactive chemicals to non polar compounds which can be eliminated from the body. The herbs such as *Zingiber officinale* (Ginger), *Allium sativum* (Garlic), *Valeriana officinalis, Passiflora incarnata, Foeniculum vulgare, Cassia senna* are found to be effective.

Table 1: Drugs useful in different phases of biotransformation

Phase I	Oxidation, reduction (Pachana)	*Zingiber officinale* (Ginger)
Phase II	Hydrolysis, Conjugation (Deepana)	*Zingiber officinale* (Ginger) *Allium sativum* (Garlic)
Phase III	Conjugation, excretion (Shodana)	*Allium sativum* (Garlic) *Cassia senna* (Senna)

***Zingiber officinale* (Ginger)**

Observations from studies on animals suggest that ginger has the ability to stimulate protective enzymes involved in xenobiotic metabolism. Thus; diets rich in some of these phytochemicals can play a major role in providing protection from xenobiotics.

Since liver is the major site of xenobiotic metabolismand transformation, stimulatory effect ofginger feedingon liver and intestine enzyme levels are significant. Othertissues namely lungs and kidney also play a role in thedetoxification and elimination of xenobiotics. The increase in GST levels in all these tissues further support

thehypothesis that regular intake of ginger in diet canenhance the activity of phase II detoxification enzymes. Quinone reductase is another important phase II enzyme which participates in the antioxidative process. Stimulation of the quinine reductase activity suggests that 5% gingerfeeding can effectively counteract the oxidative damagein tissues of liver and lungs. However, significantdifferences were not observed in kidney and intestine[15].

***Allium sativum* (Garlic)**

Several liver P-450 enzymes were examined in rats fed a diet supplemented with 1, 2, or 3 ppm Se. Compared with controls receiving 0.1 ppm Se, no significant alteration in activity was detected with respect to P-450 1A1 (responsible for DMBA activation), 1A2, 2B1, 2E1, and 3A4. In contrast, glutathione S-transferase and uridine 5'-diphosphate-glucuronyltransferase activities were elevated to a maximum of 2 to 2.5 fold in liver and kidney. As expected, there was a dose-dependent elevation of selenium concentrations in liver, kidney, mammary gland, and plasma as a function of the level of Se-garlic supplementation. The data seems to suggest that an increased detoxification of carcinogen via the phase II conjugating enzymes might represent a mechanism of tumor suppression by Se-garlic[16].

***Cassia senna* (Senna)**

Food and medicinal herbal compounds possessingrelevant antioxidant properties are xenobiotics for the human being. The hepatic endoplasmic reticulum isthe main cellular organelle responsible for thexenobiotics biotransformation and one of the sites inwhich reactive oxygen species (ROS) are generated. Thus, in this cellular organelle the biotransformationof herbal compounds and the expression of theirantioxidant properties may occur.

DISCUSSION

The manifestation of Ama (production) is inevitable as our intensity of Agni, Aaharasevanavidhi (mode of food intake), Aaharaparinamakarabhava (factors influencing digestion) may fluctuate with human influence or spontaneous deviation. Once production of ama takes place the manifestation of vyadhi (disease) is certain. On the preventive aspect as avoiding Ama is impossible the consequences of Ama can be avoided. While understanding the disease, the treatment and prevention, note on presence or absence of Ama is of high importance.

Irrespective of the subject or area of expatriation, knowledge of Ama should be known by everybody for the above cause.Knowing Xenobiotics and detoxification enhances the understanding of Ama and also gives a new perspective on relevance of periodic detoxification. The qualities of Ama and Xenobiotics seem quite similar especially with the non-absorbable and non-extractable (Asamyukta). The methods of elimination of Xenobiotics through intervention are only told in Ayurvedic texts. The polar xenobiotics can be eliminated spontaneously through urine, but the non polar lipophilic xenobiotics are be excreted through the gut in the form of Shodana (purificatory procedure) such as Virechana (Purgation) and basti (enema). The local or free toxins in the blood are also removed by raktamokshana (bloodletting) or enhanced by raktaprasadana dravya (haematonics). The toxins related to sense organs can be removed by Nasya(Nasal errhinics) and quality of biotransformation can be enhanced by raktaprasadana (haematonic), hepatotonic, hepatoprotective, agnideepaka (Promoter of digestive power) and pachakadravya (Digestive).Taking care of above qualities required for biotransformation (Amapachana and Shodana therapy) following are the interesting herbs possessing these qualities.

The *Zingiber officinale* and *Allium sativum* has the basic enzyme required for the detoxification is GST group of enzymes and specifically Cytochrome which increases GST levels (*Zingiber officinale*) and increase the activity of Cytochrome P450 *(Allium sativum)*. Since the liver is the major site of xenobiotic metabolism and transformation, the diet rich in some of these phytochemicals can give protection from xenobiotics. Quinone reductase is the important phase II enzyme present in *Zinzeber officinale* participates in antioxidative process.

Similarly the drug *Cassia senna* possesses relevant antioxidant properties helping Xenobiotic biotransformation at the level of excretion.

CONCLUSION

Any toxins that are not owned by the body, but produces toxic effect is called as Xenobiotics. These possess mutagenic, teratogenic, carcinogenic effect. Ama is initially manifested as undigested material, but it has a very complex form. Apachitaanna rasa (indigestion of ingested food) turns Amarasa. This asamyukta (inassimilable) amadosha ferments and putrefies abhishyandi (oozing) gunayuktaamavisha. The Ama is a toxin of both endogenous and exogenous origin. In this way Ama and Xenobiotics share similar qualities. Both Ama and Xenobiotics are tough for spontaneous elimination. They need a special pathway and intervention that facilitates the elimination.

Bio transformation refers to series of biochemical reactions occurring in the body to convert the foreign (often toxic) compounds to non toxic or less toxic and more easily excretable forms. Man is continuously exposed to several foreign compounds such as drugs, pollutants, food activities, cosmetics, pesticides, unwanted compounds produced in large intestine by bacteria, waste materials produced in normal metabolism which are toxic and hence to be eliminated quickly from the body. Biotransformation of Xenobiotics takes place mainly in Liver which is equipped with enzyme machinery, Kidney and other organs Therefore one can enhance the process of biotransformation by periodic Shodhana (purificatory therapy) and adequate use of hepatoprotective drugs to enhance detoxification.

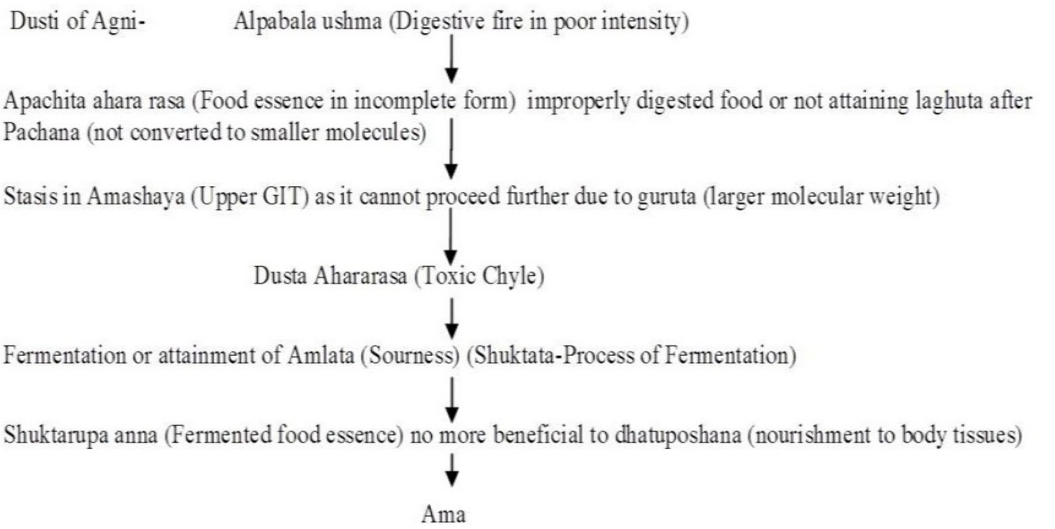

Figure 1: Biochemistry of Ama

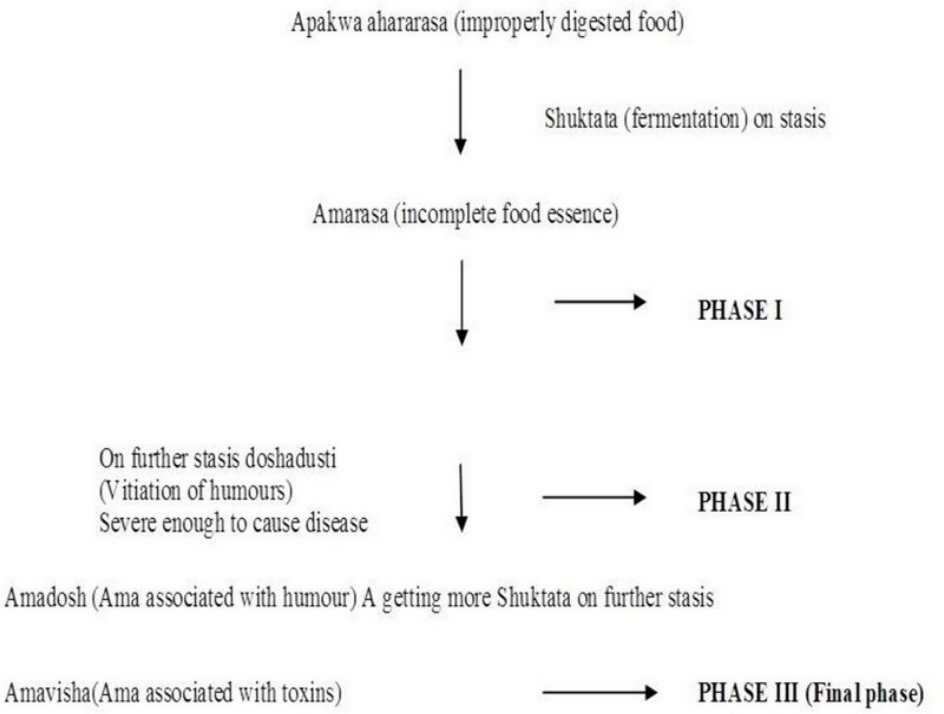

Figure 2: Formation of Amarasa, Amadosha, Amavisha in Course of Time[4]

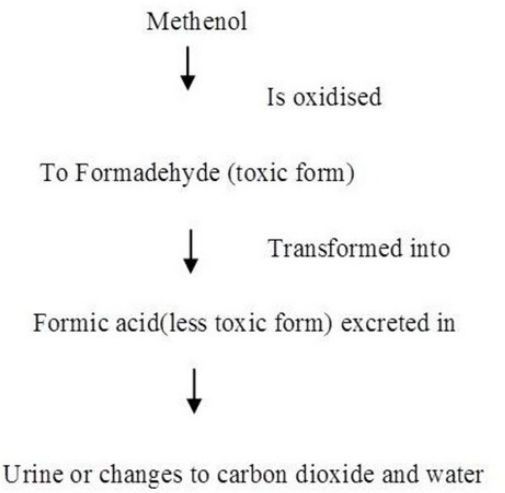

Figure 3: Oxidation

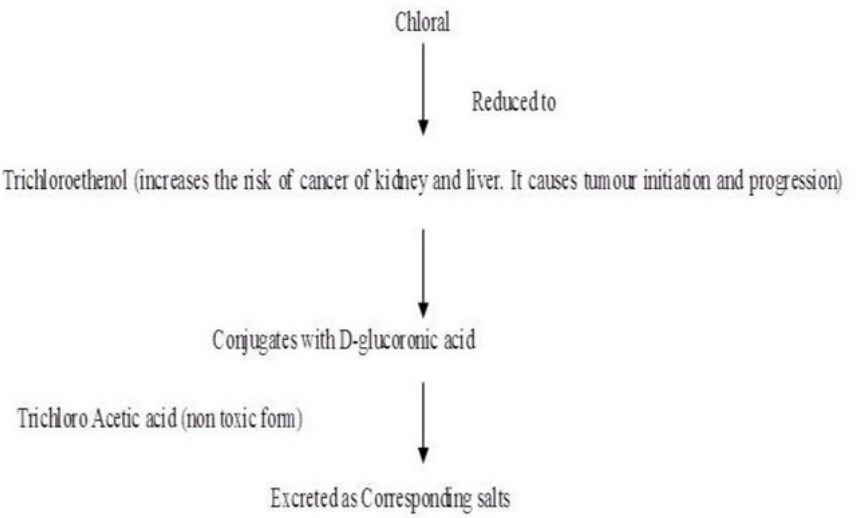

Figure 4: Reduction As Pachana (Digestion) : Removal of oxygen and gain of Hydrogen, gaining of electron [13]

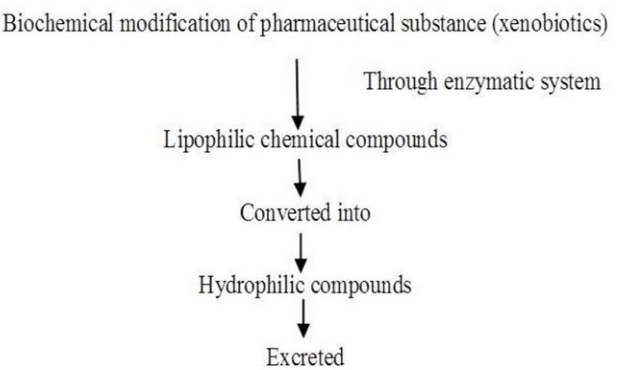

Figure 5: Conjugation

The method of elimination of ama and Xenobiotics can be assessed only with the aid of Ayurveda concepts. Modern biochemistry explains the elimination of polar Xenobiotics (water soluble) through urine. But the method of elimination of nonpolar or lipophilic Xenobiotics can be possible only by Ayurveda. That is as fat cannot be eliminated from urine, but can be brought to intestine and then eliminate by virechana and so on.

Apart from that drugs like *Zingiber officinale* (Ginger), *Allium sativum* (Garlic) has to be used to enhance the process of biotransformation and also avoid Ama and mala sanchaya

Scope for Further Research

- Study can be conducted on the concept of Xenobiotics for reconsideration as Ama.
- Can be worked on lines of developing Objective parameters for the description of biochemistry of Ama by laboratory methods.

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