
Is Chronic Combination Therapy of HAART and α -ZAM, Herbal Preparation for HIV Infection Safe?

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<http://dx.doi.org/10.5772/50509>

1. Introduction

Since discovery of acquired immunodeficiency syndrome (AIDS) and subsequent isolation of the virus (HIV) more than 30 million have been infected [1]. Sub-Saharan Africa was affected most with HIV infection with estimated 2/3rd of the World's HIV infected people. Nigeria is the largest populated country in Africa and it was estimated that about 3 million of the population is infected with human immunodeficiency virus [2]. Thus Nigeria is the second largest country after South Africa with largest HIV infected population in the World [1]. Nigerians like any other people in Africa are favourable to the use of herbal remedies for major illnesses, thus, that HIV infection has no cure medically serves as a catalyst to source for cure in herbal remedies [3].

Herbal remedies which are considered as herbs, herbal materials, herbal preparations and finished herbal products, that contain as active ingredients parts of plants, or plant materials, or combinations thereof used to treat a multitude of ailments throughout the world¹. Because many HIV patients denied the use of herbal products when asked by medical practitioners, the safety of combination therapy of orthodox drugs and herbal remedies had been a major concern to many people especially when the chemical constituents of the latter product are not known and would be used for a long period [4, 5].

There was no doubt about the effectiveness of herbal remedies in HIV infection. There are many classes of herbal remedies used for HIV infection based on chemical constituent: alkaloids, carbohydrates, coumarins, flavonoids, lignans, phenolic, proteins, quinones, terpenes and tannins. There are many herbal remedies that have been found to inhibit one or more steps in HIV replication [6, 7]. Alkaloids derivatives herbal remedies (e.g. *Ancistrocladus*

korupensis) from tropical liana plant inhibit reverse transcriptase and HIV induced cell fusion [8]. p14 (HIV tat regulatory protein that activates transcription of proviral DNA) had been documented to be inhibited by a carbohydrate derivative, pentosan poly-sulphate [9]. A coumarin herbal remedy in form of canolides from tropical forest tree (*Calophyllum lanigerum*) was rated as non-nucleoside reverse transcriptase inhibitor in potency [10]

However, every drug is a potential poison. Thus some herbal remedies are toxic especially when used over a long period. Despite alkaloid containing herbal remedies had been found to be very effective in HIV infection however some michellamines group of alkaloid were found to be cytotoxic thus limiting them for therapeutic use [11]. Quinones and xanthenes derivatives herbal remedy were weakly effective against HIV infection and the proved effective medications were cytotoxic [10, 12].

Because HIV infection is a terminal illness, there is an increase in use of herbal remedy in Nigeria [13]. Many HIV patients resulted to herbal therapy at the on-set of HIV diagnosis before commencement of highly active antiretroviral therapy (HAART) while some use it as complementary therapy [14, 15]. The major concern is possible negative drug interaction of herbal therapy and HAART. It was documented that garlic and St John's wort negatively interact with HAART [16].

The fact that many consumers could not distinguish between the safe herbal drugs from potential harmful led to general acceptance or rejection of herbal therapy. A safe herbal therapy may become harmful if used for a long period. African potato (*hypoxis*) and *Sutherlandia frutescens* have been documented to be harmful when used for a long period with HAART [17]. Even chronic herbal derived vitamins and cannabis use were established to negatively influence hepatic metabolism of HAART components [18].

However, some herbal remedies have been documented to be beneficial when used with orthodox medicines. Coumarin derived herbal remedies decreased drug resistance resulting from HIV mutation associated with non-nucleoside analogue-nevirapine [19, 20]. Some herbal remedies have also shown to decreased toxicity associated with HAART. The hepatic toxicity associated with acetaminophen was reduced by *Gentiana manshurica* [21]

There are many herbal remedies that are used in Nigeria for HIV infection. Many of them are complementary to HAART. Toxicological studies have been done on many herbal products in Nigeria using animal models [22]. Unlike the assumptions that herbal remedies are harmless because of the natural source, many have been found to be toxic [23]. Thus, the researchers are trying to identify the safe herbal remedies and encourage its use while discouraged the harmful herbal products [24].

The beneficial effect of combination therapy of HAART and α -Zam an herbal remedy used as alternative therapy for HIV infection had been documented at acute and sub-acute phase [25]. The use of herbal remedy as alternative therapy to HAART had met a lot of criticisms especially when such medication has not passed through all the phases of drug trial. It is not uncommon that some HIV patients taking HAART are also using alternative herbal remedy simultaneously without the knowledge of both herbal therapist and medical practitioners

[26]. However, the benefits in association with potential toxicity of such complementary therapy at chronic phase needed an evaluation.

2. Materials and method

The materials and method had been described in earlier studies [5, 20, 22]

2.1. A-zam

This is herbal concoction that contained alkaloids, saponins, tannins, cardenolides and possibly anthraquinones [5]

2.2. Highly Active Anti-retroviral Therapy (HAART)

The drugs used in this study were Nevirapine (50mg/kg), Lamivudine (100mg/kg) and Zidovudine (300mg/kg) prepared by grinding the tablets into fine powder.

2.3. Drug preparation

10% of the herbal preparation was made to using tepid distilled water as recommended for use by herbal therapist. A fresh preparation was prepared daily.

2.4. Animals

90 male wistar rats (150-200g body weight) were acclimatised for 7 days before the start of the experiment. Throughout the time of the experiment, they were housed under standard environmental conditions, maintained on a natural light and dark cycle. The animals had free access to rat chow and portable water.

2.5. Drug administration

The freshly prepared herb and HAART were administered orally using oral canula to animals once in 24 hours. The herbal preparation and HAART (nevirapine, zidovudine and lamivudine) were administered concurrently to the groups (40 rats) receiving combination Therapy while another 4 groups (40 rats) received graded concentrations of herbal remedy alone. Animals were deprived of food before drug administration after which they were allowed access to food.

2.6. Experimental procedure

A pilot toxicity study was earlier carried out by a single dose administration of herbal preparation to rats. Results showed that neither mortality nor change in behaviour was observed even at 3200mg/Kg body weight (Onifade et al 2011). 90 wistar rats was randomised divided into 9 groups (10 rats per group) and were administered once daily for 84 days with Herbal concoction of 400mg/kg, 800mg/kg, 1600mg/kg, 3200mg/kg, 400mg/kg+HAART,

800mg/kg+HAART, 1600mg/kg+HAART, 3200mg/kg+HAART, 400mg/kg + HAART (Nevirapine, Zidovudine & Lamivudine), 800mg/kg+ HAART (Nevirapine, Zidovudine & Lamivudine) respectively. The 9th group served as control thus received rat chow and water only. All the animals were allowed to free access chow, water, fresh air and move freely. They were monitored daily for feeding pattern, behavioural or physical changes. 24 hours after the last dose (the 85th day), the diethyl ether anaesthetised animals were bled from the retro orbital plexus for haematological (total white blood cell count, red blood cell count, haemoglobin concentration, platelet count and lymphocyte counts), serum biochemical analysis (electrolytes, urea, creatinine, lipid profile, liver and renal functions tests), fertility profiles (follicle stimulating hormone, progesterone, leutenising hormone, Oestrogen, testosterone and prolactin) and sperm motility test. The liver, kidney, spleen, skin, heart and bone marrow were harvested for histological changes.

3. Results

The results were categorised as follows:

OBSERVATION- No physical or behavioural abnormalities were observed in all the groups of animals throughout the study.

LABORATORY- This is outlined into haematological, clinical chemistry (liver and renal function tests and lipid profile), fertility (fertility profile and sperm analysis) and histological results.

| Substance administered | Leucocyte | Red blood cell (x 10 ⁶) | Haemoglobin (g/dl) | Platelet (x10 ⁵) | Lymphocyte % | Lymphocyte total |
|------------------------|-----------|-------------------------------------|--------------------|------------------------------|--------------|------------------|
| Ratchow& water | 6400±334 | 7.55±1.2 | 13.4±2.1 | 3.81±1.9 | 68±6 | 4352±124 |
| 400mg/kg α-zam | 9600±228* | 8.34±0.7 | 15.3±1.8 | 7.19±2.56 | 84±9 | 8064±2365* |
| 800mg/kg α-zam | 9400±887* | 7.88±0.56 | 14.3±1.2 | 9.65±2.85 | 85.6±8 | 8084±1890* |
| 1600mg/kg α-zam | 9700±934* | 7.14±0.34 | 13.5±1.1 | 11.09±4.0 | 72±7.2 | 6984±459 |
| 3200mg/kg α-zam | 6200±415 | 7.42±0.09 | 14.3±1.5 | 8.0±2.3 | 69±4.4 | 4278±234 |
| 0.4g/kg α-zam +HAART | 7200±330 | 7.3±0.8 | 15.1±1.2 | 5.7±2.1 | 72±8.1 | 4100±350 |
| 0.8g/kg α-zam +HAART | 8000±720 | 7.2±0.9 | 15±1.4 | 6.8±1.8 | 70±6.4 | 4000±270 |
| 1.6g/kg α-zam +HAART | 6500±635 | 7.74±0.78 | 15.0±1.3 | 7.93±1.8 | 65±5.9 | 4225±519 |
| 3.2g/kg α-zam +HAART | 6600±756 | 7.22±0.82 | 14.6±1.6 | 5.56±1.7 | 70±3.7 | 4620±418 |

*- statistically significant

Rat chow and water only is the control and reference group

Table 1. Showing the Haematological parameters using α- Zam alone and in combination with HAART (mean and standard deviation)

Clinical chemistry- This is divided into 2: Electrolytes, urea and creatinine (Renal functions tests) and Liver functions tests and lipid profile

| Substance Administered | Na+ | K+ | HCO ₃ ⁻ | Cl ⁻ | Urea | Creatinine |
|------------------------------|---------|----------|-------------------------------|-----------------|----------|------------|
| Rat chow and water | 142±2.0 | 4.5±0.31 | 30±2.2 | 103±2.4 | 6.7±0.54 | 62±2.1 |
| 400mg/kg α -zam | 140±2.1 | 4.6±0.22 | 30±2.1 | 104±2.3 | 6.5±0.46 | 64±2.5 |
| 800mg/kg α -zam | 144±2.7 | 4.4±0.27 | 30±2.0 | 105±1.9 | 6.6±0.32 | 66±1.9 |
| 1600mg/kg α -zam | 143±1.5 | 4.5±0.34 | 28±2.7 | 103±2.9 | 6.8±0.45 | 65±2.3 |
| 3200mg/kg α -zam | 144±2.0 | 4.6±0.21 | 31±0.9 | 102±2.8 | 6.9±0.3 | 63±1.8 |
| 0.4g/kg α -zam+HAART | 143±1.9 | 4.6±0.3 | 27±3.1 | 104±2.2 | 6.7±0.5 | 66±3.2 |
| 0.8g/kg α -zam +HAART | 142±2.1 | 4.6±0.2 | 29±2.9 | 103±3.4 | 6.6±0.4 | 65±2.2 |
| 1.6g/kg+HAART α -zam | 141±2.9 | 4.7±0.18 | 30±1.1 | 104±2.3 | 6.6±0.4 | 64±1.7 |
| 3.2g/kg +HAART α -zam | 142±1.8 | 4.7±0.21 | 31±0.7 | 103±2.7 | 6.8±0.55 | 65±2.1 |

Rat chow and water only is the control and reference group

Table 2. Showing the Electrolytes, Urea and Creatinine using α - Zam alone and in combination with HAART (mean and standard deviation)

| substance administered | albumin | globulins | AST | ALT | Total protein | HDL | Triglyceride | LDL | Total cholesterol |
|-------------------------------|---------|-----------|--------|--------|---------------|----------|--------------|---------|-------------------|
| Rat chow and water | 31±5 | 52±5 | 51±7 | 11±2 | 83±13 | 1.1±0.2 | 0.8±0.3 | 0.4±0.2 | 1.8±0.13 |
| 400mg/kg α -zam | 35±4 | 58±4 | 45±7.8 | 9±2.1 | 92±4.9 | 1.2±0.4 | 0.8±0.3 | 0.4±0.2 | 1.9±0.23 |
| 800mg/kg α -zam | 34±4.4 | 59±4 | 49±6.9 | 12±2.3 | 93±2.7 | 1.3±0.3 | 0.7±0.29 | 0.4±0.1 | 1.8±0.19 |
| 1600mg/kg α -zam | 32±2.3 | 57±4 | 54±4.3 | 14±3.2 | 89±4 | 1.1±0.35 | 0.8±0.36 | 0.3±0.1 | 1.8±0.17 |
| 3200mg/kg α -zam | 30±3.2 | 61±3* | 56±3 | 13±1.9 | 91±5 | 1.4±0.19 | 0.6±0.38 | 0.4±0.1 | 1.9±0.11 |
| 0.4g/kg α -zam +HAART | 34±3.2 | 57±6 | 49±4 | 12±2.2 | 86±6 | 1.3±0.9 | 0.8±0.26 | 0.4±0.1 | 1.7±0.1 |
| 0.8g/kg α -zam + HAART | 33±2.7 | 56±5 | 52±9 | 12±1.8 | 85±7 | 1.3±0.2 | 0.7±0.3 | 0.4±0.2 | 1.7±0.1 |
| 1.6g/kg α -zam +HAART | 33±2.9 | 58±4 | 52±4 | 11±0.7 | 91±5 | 1.2±0.21 | 0.7±0.27 | 0.3±0.1 | 1.7±0.24 |
| 3.2g/kg α -zam +HAART | 34±1.8 | 57±5 | 53±5 | 12±1.1 | 91±6 | 1.3±0.17 | 0.7±0.26 | 0.4±0.1 | 1.8±0.23 |

Rat chow and water only is the control and reference group

Table 3. Showing the LIVER FUNCTIONS TEST AND LIPID PROFILE using α Zam alone and in combination HAART (mean and standard deviation)

| Substance administered | Follicle Stimulating Hormone (miu/ml) | Leutenizing Hormone (miu/ml) | Prolactin (ng/ml) | Estradiol (pg/ml) | Progesterone (ng/ml) | Testosterone (pg/ml) |
|-----------------------------|---------------------------------------|------------------------------|-------------------|-------------------|----------------------|----------------------|
| Rat chow and water only | 2.4±0.2 | 4.4±0.22 | 16.2±0.4 | 110±9 | 10.1±2.3 | 7.1±0.1 |
| 400mg/kg α -zam | 2.8±0.1* | 4.9±0.23* | 16.9±0.3 | 114±8 | 10.2±2.1 | 7.8±0.2* |
| 800mg/kg α -zam | 2.7±0.11* | 4.8±0.3 | 16.3±0.2 | 111±3 | 9.9±1.9 | 7.7±0.2* |
| 1600mg/kg α -zam | 2.7±0.12* | 4.7±0.23 | 16.5±0.1 | 112±4 | 10.0±1.7 | 7.8±0.3* |
| 3200mg/kg α -zam | 2.9±0.2* | 4.9±0.27 | 15.9±0.4 | 110±5.6 | 10.1±1.1 | 7.9±0.32* |
| 0.4g/kg α -zam+HAART | 2.7±0.2 | 4.5±0.3 | 16.5±0.3 | 111±6 | 10.3±2.2 | 7.5±0.3 |
| 0.8g/kg α -zam+HAART | 2.6±0.2 | 4.5±0.1 | 16.3±0.1 | 111±9 | 10.2±1.8 | 7.5±0.3 |
| 1.6g/kg+HAART α -zam | 2.6±0.2 | 4.6±0.21 | 16.1±0.3 | 112±1.8 | 10.2±2.5 | 7.6±0.23 |
| 3.2g/kg+HAART α -zam | 2.5±0.2 | 4.5±0.18 | 16.3±0.3 | 112±2.7 | 10.3±3.1 | 7.5±0.21 |

*- statistically significant

Rat chow and water only is the control and reference group

Table 4. Showing the FERTILITY PROFILE using α -Zam alone and in combination with HAART (mean and standard deviation)

| Substance administered | Motility (%) | Live/dead (%) | Volume (ml) | Count ($\times 10^7$) |
|-----------------------------|--------------|---------------|-------------|-------------------------|
| Rat chow& water | 66±27 | 97±2 | 5.2±0.1 | 141±21 |
| 400mg/kg α -zam | 54±22 | 95±3 | 5.2±0.1 | 100±34 |
| 800mg/kg α -zam | 74±23 | 95±4 | 5.2±0.1 | 130±15 |
| 1600mg/kg α -zam | 60±12 | 92±8 | 5.1±0.1 | 114±41 |
| 3200mg/kg α -zam | 72±21 | 96±3 | 5.2±0.1 | 125±31 |
| 0.4g/kg α -zam+HAART | 67±24 | 98±4 | 5.1±0.2 | 142±27 |
| 0.8g/kg α -zam+HAART | 69±21 | 98±3 | 5.1±0.2 | 145±36 |
| 1.6g/kg α -zam+HAART | 66±27 | 99±2 | 5.1±0.1 | 147±27 |
| 3.2g/kg α -zam+HAART | 64±22 | 97±4 | 5.1±0.1 | 144±9 |

Rat chow and water only is the control and reference group

Table 5. Showing the sperm count using α -Zam alone and in combination with HAART (mean and standard deviation)

| Substance administered | Histological Changes-Skin | Histological Changes-Spleen | Histological Changes-Testes | Histological Changes-Liver | Histological Changes-Kidney | Histological Changes-Bone Marrow |
|------------------------------|---------------------------|-------------------------------------|-----------------------------|----------------------------|---|----------------------------------|
| Rat chow and water only | No remarkable changes | No remarkable changes | No remarkable changes | No remarkable changes | No remarkable changes | No remarkable changes |
| 400mg/kg α -zam | No remarkable changes | Mild congestion of splenic plexuses | No significant changes | Mild atrophy | Mild tubular atrophy and focal necrosis | Hyper-cellular marrow |
| 800mg/kg α -zam | No remarkable changes | Mild congestion of splenic plexuses | No significant changes | Mild atrophy | Mild tubular atrophy and focal necrosis | Hyper-cellular marrow |
| 1600mg/kg α -zam | No remarkable changes | Mild congestion of splenic plexuses | No significant changes | Mild atrophy | Mild tubular atrophy and focal necrosis | Hyper-cellular marrow |
| 3200mg/kg α -zam | No remarkable changes | Mild congestion of splenic plexuses | No significant changes | Mild atrophy | Mild tubular atrophy and focal necrosis | Hyper-cellular marrow |
| 0.4g/kg α -zam+ HAART | No histological changes | Normal splenic histology | Normal testicular tissue | Normal liver anatomy | Mild focal necrosis | Normal cellularity |
| 0.8g/kg α -zam+HAART | No histological changes | Normal splenic tissue | Normal testicular tissue | Normal liver anatomy | Mild focal necrosis | Normal cellularity |
| 1.6g/kg+HAA RT α -zam | No remarkable changes | Mild congestion of splenic plexuses | No significant changes | Mild atrophy | Mild tubular atrophy | Hyper-cellular marrow |
| 3.2g/kg+HAA RT α -zam | No remarkable changes | Mild congestion of splenic plexuses | No significant changes | Mild atrophy | Mild tubular atrophy | Hyper-cellular marrow |

Table 6. Showing the histological changes of A-Zam with HAART

4. Discussion

The effect of combination of drugs may manifest in acute or chronic phase. The acute or chronic manifestation of drug toxicity may be mild or lethal which may even result in death.

Although the combination of herbal medications with orthodox drugs had caused beneficial effects like reduction in side effects of the latter but the chronic toxicity is very fatal [21]. From the result above, none of the animal had physical or behavioural impairment thus only laboratory analysis could indicate the potential harmful effects of the combination therapy of HAART and the herbal concoction.

The fact that the animal is feeding or behaving normally does not guaranteed the total well-being especially when taking medication for a long period [25]. Although the physical and behavioural changes of the animal had to be compared with control group but there may be silent damage to cells, tissues or organs that has not manifested as systemic derangements. The health status of the animal taking potential harmful drugs can be confirmed by assessing the major laboratory parameters that are normally grouped into haematological, renal function, liver functions, lipid profiles, fertility profiles and histology of all the major organs [26].

Haematological profiles normally showed the erythrocyte, leucocyte and platelet but the apparent functionality of the immune system (lymphocyte and granulocyte) can also be obtained. When the herbal remedy was used alone in this study, there was leucocytosis with lymphocyte predominance as shown in Table 1. The lymphocyte predominance gradually changed to granulocytes as concentration increases and peak at 1600mg/kg. However, there was normal leucocytes differential irrespective of the dose when combined with HAART. There was also bone marrow hyper-cellularity when herbal medication alone was administered but normalised with HAART as shown by histological changes in Table 6. This confirmed that herbal induced leucocytosis was ameliorated by HAART induced leucopenia [21, 22]. This showed that combination of this herbal remedy with HAART for HIV infection is beneficial if used for longer period.

Decrease in erythropoiesis (anaemia) that usually manifest early when potential bone marrow suppressive drug was administered for long period was absent with α -zam alone or combination therapy [25]. It was evident from table 1 above that the herbal remedy did not affect erythropoiesis negatively as evidenced by normal haemoglobin concentration and red cell blood count. However, A-Zam herbal remedy is associated with thrombocytosis. The platelet count increased gradually with increase in A-Zam concentration. The combination therapy of A-Zam with HAART caused significant decrease in platelet count. Thus bone marrow suppression effects of HAART components normalised the potential thrombocytosis as shown in Table 1. Chronic use of A-Zam alone or in combination therapy with HAART has no harmful effect on haematological parameters rather ameliorating side effects of associated traditional and orthodox medicines.

The role of kidney in drug excretion cannot be overemphasised. Any negative interaction of drug(s) may affect its clearance from the body. Thus, it is not unusual to noticed renal impairment while other organs and systems perform normally [26]. The combination of two potential harmful drugs may worsen the renal architecture. It was established that many of the antiretroviral therapy are potential nephrotoxic and becomes more pronounced when

used in combination with another drug with similar deleterious effect ^[28]. Renal functions were not impaired when A-Zam alone or in combination with HAART as shown in Table 2 although mild histological changes that reduced with complementary therapy in Table 6 were observed. This study depicted a neither harmful nor beneficial effect of combination of 2 potential harmful drugs used for HIV infection ^[29].

Drug metabolism is majorly handled by liver. Any toxic drug will likely impair hepatic functions. Some drugs induce hepatic enzymes and apparatuses that accelerate metabolism ^[30]. This increases fast elimination of the toxic drug from the body. However, some drugs inhibit cytochrome P-450 thus delaying its hepatic clearance of such medication ^[31]. The danger is combination of cytochrome P-450 inhibitors or inducers. Table 3 showed that both HAART and herbal remedy (A-Zam) are not hepatotoxic alone or in combination. Although there were mild atrophic changes in the liver when A-Zam was used alone but the damage did not caused any significant increase in both cytosolic and mitochondrial hepatic enzymes. This result showed one of the silent cellular injuries that resolved favourably therefore not showing any plasma changes.

The metabolic status of individual is very important. The metabolic disorders associated with lipid derangement in adult are fatal. Some drugs have been noted to cause hyperlipidaemia (especially low density cholesterol and triglyceride) therefore potentiating Raeven's syndrome in adulthood ^[28]. The coronary index is better with hyperlipidaemia of high density proportion ^[30]. Any drug that lowers HDL will cause harmful effect and increases coronary index ^[28]. From the result in table 3, neither A-Zam alone nor its combination with HAART caused any significant harmful hyperlipidaemia. This confirmed that complementary therapy (A-Zam and HAART) is cardio-protective.

Average adult male is conscious of his fertility profile and sperm analysis. Infertility has been a major concern especially when the fault is associated with male. Many drugs affect fertility of male therefore complementary therapy of such medications constitute danger ^[28]. Spermatogenesis is influenced by hormonal changes. Table 4 showed deranged follicle stimulating hormone (FSH) and testosterone in rats with A-Zam therapy portraying a potential danger. However, combination of HAART with A-Zam ameliorated the fertility hormonal changes which was collaborated with sperm sperm analysis (total sperm count) in Table 5. Plasma and semen analysis showed derangement which did not manifested with significant testicular injury as shown in table 6.

The histology of heart and skin as shown in table in Table 4 were not affected by herbal remedy or its combination with HAART. This confirmed the earlier studies that some herbal remedy are not dermato-toxic ^[25, 32]. Despite there was no significant changes in liver and renal functions parameters, it was clearly evident there were mild injury to kidney and liver with chronic A-Zam administration alone. However, complementary therapy of HAART and A-Zam reduced the toxic injuries on liver, kidneys and bone marrow. This histological result in confirmed the safety of chronic complementary therapy of HAART and A-Zam as documented in earlier studies ^[20, 33].

5. Conclusion

This study concluded that the chronic complementary therapy of herbal remedy (A-Zam) with HAART is safe and beneficial as evidenced by side effects amelioration of both orthodox and traditional medicines in wistar rat in this study.

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