

Original article:

Exploration of Unani concept of blood purifying drugs and likely models for its screening

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Abstract

Introduction: In Unani system of medicine, blood is regarded as mixture of *akhlat* (humours) i.e. *dam* (Sanguine), *balgham* (phlegm), *saфра* (yellow bile) and *sawda* (black bile). Normal blood consists of “*akhlata latifa* (plasma)” and “*kaseefa* (corpuscles)”. Normal blood is one in which all humours are in normal proportion in terms of quantity and quality and specific to each individual. It is normal in colour, free from bad odour and moderate in viscosity. Morbid blood develops due to impurities /disease in the blood which ultimately alter its quantity and quality. If we co relate these abnormalities with modern concept then all bleeding disorders and coagulopathy fall under “*Riqqate dam*” (low viscosity of blood); all the thromboembolic disorders; polycythaemia, leukaemia and anaemia fall under “*Ghilzate dam*”(hyperviscosity of blood), while septicaemia, bacterial diseases can be correlated with “*ufunat*” (infections).

Methods: The classic and relevant books of Unani and conventional medicine were studied. The databases utilized for obtaining information, are scientific research publications from indexed journals available through Google Scholar, PubMed and Science Direct. **Results and Conclusion:** Blood purifying drugs cause necessary changes and maintain the viscosity of the blood by their moderate heat; cold; dry and wet properties. These drugs are alterative and bring the quality and quantity of blood in equilibrium. Strengthen the defensive mechanism and eliminate toxins via sweat, urine, faeces etc. These drugs are digestive, tonic to stomach and liver and boost the immune system. In the line of the above conceptual framework few experimental models are being suggested i.e. effect of drugs on blood constituents, coagulation parameters, anemia, leukaemia, polycythaemia, thrombocytopenia and infections. This preliminary study may serve as a tool for the screening of blood purifier drugs in various blood disorders.

Keywords: *Impure blood; Blood disorders; Unani concept; Experimental study; Blood purification*

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Introduction

In Unani system of medicine blood is regarded as a mixture of all humours i.e. sanguine, phlegm, yellow bile and black bile. Normal blood is one in which these four humours are in equal proportion with respect to their quantity and quality which is specific to each healthy individual.^{1,2} Thus any alteration in the quality and quantity of any of four humours in particular person makes the whole blood abnormal.¹ Unani physicians state that morbid blood is caused

by alteration in its temperament. The abnormal temperament means the quantity of matter with its kaifiyat (hot, cold, moist, dry) exceeds from its normal proportion or any abnormality in humours.^{3,4} Ibn Rushd (1126-1198 A.D) mentioned that temperament of organ remains in its normal proportion when the blood which provides nutrition to it remains normal. This is only possible when the temperament of digestive organs is normal.⁵ Proper functioning of liver, stomach, kidney and spleen is necessary for the

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production of normal blood. When the function of the liver is disturbed due to alteration in its temperament it ultimately affects the production of humours and also alters the quality and quantity of it.⁵

Hematological disorders are quite frequent in all age group ranging deficiency disorder to relatively rare multiple myeloma.⁶ The magnitude of benign hematological disorders in India is shocking. Acquired hematological disorders occur due to iron and vitamin deficiency which indeed exceeds the congenital causes.⁷ In the United States approximately 10,000 deaths were attributed to blood diseases in 2010. In which 1,900 were because of coagulation defects, 800 were due to purpura and 2,400 by other blood diseases.⁸ Treatment include corticosteroid therapy, blood transfusion, plasmapheresis, surgery, bone marrow cell transplant and life style changes. None of these treatments alone offer an alternative for the definitive cure for blood diseases and the majority of treatments also have side effects.⁹ There is no direct description of modern hematological diseases in ancient Unani classics; however, this does not mean that Unani medicine has not confronted with hematological diseases. Elaboration on signs and symptoms of traditional diseases elucidate their similarity to modern hematological diseases. Pathological changes that occur in various blood diseases are nearly parallel to morbid blood.

The valuable information about the concept of blood purifying drugs is scattered in the Unani literature, with different views pertaining to interpreting blood purifying drugs. In Unani system of medicine morbid blood is entertained only for skin diseases and blood purifying drugs show favorable outcomes in many of the skin ailments. A number of researches have also been carried out in this area¹⁰⁻¹¹ but the above mentioned aspect is totally untouched by the Unani physicians and researchers. In this study all the relevant literature to blood purification and blood purifying drugs are compiled and explained in systematic way to minimize the differences in understanding of this core concept. This preliminary study not only explores the concept of blood purification but also sheds light on its potential in the management of blood anomalies.

Methodology

Survey of literature for concept of blood purification

An extensive search was carried out of Unani literature for concepts of blood, morbid blood and blood purifier drugs. All the Unani classical books and discussion with experts were conferred with for this study. Much emphasis has been given on its meaning,

different views of Unani physician, mechanism of action, indications, therapeutic uses, present scenario and future research etc. Contemporary reference books, relevant articles, periodicals, peer reviewed indexed journals and other published work on Pub med, Science Direct, Google scholar etc. were surveyed to find out on going current theories and advancement in the field of hematology.

Criteria evaluation

Normal blood was defined with the help of Unani literature. Any derangement in the quantitative or qualitative determinants of blood was noted down and accordingly the criteria for blood purifying drugs were charted out.

Survey of models for screening of blood purifying activity

Animal models were searched in the various books of experimental pharmacology and relevant indexed journals in the light of the concept of morbid blood and its types, principles of treatment and mechanism of blood purification of Unani drugs. The models noted were explored in reference of the determinant searched from the Unani literature.

Suitability of existing models

After survey of literature a correlation of animal models and its suitability was ascertained in the light of Unani concept.

Evaluation of suitable models

On the basis of the criteria, several animal models were selected for the screening of blood purifying drugs which include effect of drugs on blood composition; anaemia; polycythaemia; thrombocytopenia; thrombosis; leukaemia; hyperlipidaemia and blood coagulation. These models are presently applied to screen drugs for various blood anomalies.

Validation and reliability of the selected models

From literature survey of morbid blood, mechanism of blood purification of Unani drugs was determined. The criteria for suitability of the animal models to screen the blood purifying drug activity were developed. The suitable tests were enumerated and their advantages were detailed.

Results

Concept exploration: Characteristics of normal blood and morbid blood

Regarding concept of blood, literature illustrates that blood is a mixture of all four humours *i.e.* sanguine, phlegm, yellow bile and black bile. Normal blood is one in which all humours are in normal proportion with respect to their quantity and quality and specific to each individual. It should be normal in colour, free from bad odour, moderate in viscosity and taste, free from putrefaction and acidity.^{4,12,13} Morbid blood

develops due to impurities or disease in the blood which ultimately alter its quantity and quality. Blood may become viscous, morbid, watery, black and sometime white. Whitish colour is due to addition of phlegm which is cold when compared to normal blood. Blackish colour is due to addition of black bile or excessive heat making it warmer than normal blood. Morbid blood may also affect its odour. It may be due to addition of any abnormal humour or due to infection in blood itself. The consistency of blood is also altered and it becomes viscous due to excessive phlegm and black bile or watery due to yellow bile.⁴

Concept of blood purifying drugs

While going through the Unani literature it was noted that nearly all the blood purifying drugs are bitter in taste and hot and dry in second degree. These drugs are characterized by lenitive, detergent, laxative, deobstruent, alterative and irrigator properties. Because of these properties blood purifying drugs act as digestive, tonic to stomach and liver, diuretic, antiseptic, antipyretic and tonic to vital organs. Whereas elucidating its mechanism of action it was established that blood purifying drugs cause necessary changes in blood and remove its waste material so that the blood is purified from its impurities. Blood purifying drugs restore the normal viscosity of blood by their moderate heat, cold, dry and wet properties. These drugs bring the quality and quantity of humours or blood in equilibrium; produce and maintain normal blood by neutralizing the excessive heat of blood due to their alterative and moderate hot (*lateef hararat*) and dry properties. These drugs strengthen the defensive mechanism and prevent the body from toxins. They boost the immune system; normalize the blood composition and tone up the sluggish liver and kidney for its normal function. Blood purifying drugs eliminate toxicity of blood via sweat, urine, faeces etc. and internally cause some changes in blood; kill the morbid matters and purify the blood.^{14,15,16}

Correlation with the present concept

Blood becomes abnormal due to alteration in its composition. Alteration occurs both in quantity and quality.^{17,5} Quantity of blood may be increased or decreased while in quality viscosity of blood either increased or decreased or it may be infected due to toxins. If we correlate these abnormalities with modern concept of blood diseases then all bleeding disorder and coagulopathy fall under decreased viscosity of blood. Thromboembolic disorders, hyper coagulability, polycythaemia, leukaemia, anaemia, hyperlipidaemia and hyperglycemia fall under increased viscosity of blood, while septicaemia,

toxaemia and other infectious diseases can be correlated with infections.

Criteria for screening of blood purifying activity

After extensive search of the literature it was noted that Blood purifier drugs act in several ways. (Table 1) Therefore, in the light of their mechanism some criteria (Table 2) have been selected for the screening of blood purifying activity of Unani drugs.

2 Discussion

According to Unani concepts, liver is the principal producer of many of the blood constituents. Spleen, kidney and gall bladder keeps blood clean. Proper functioning of these organs is necessary for production and maintenance of normal blood. When the function of the liver is disturbed it ultimately affects the production of blood and also alters its quality and quantity. A pathological change that occurs in morbid blood also depends upon surplus addition of other humours and changes the morphology of blood.³

There is no exact description of modern hematological diseases in ancient Unani classics; however, this does not mean that Unani medicine has not been confronted with hematological diseases. There is a description for blood diseases in Moalijate Buqratia,¹⁴ Firdausul Hikmat(775-890 AD)¹⁶ and Tibbe Akbar(1721 AD).¹⁷ Pathological changes that occur in hematological diseases are highly correlated to morbid blood and signs and symptoms of blood diseases are almost similar to signs and symptoms of morbid blood. Spleenomegaly is the crucial diagnostic sign in all diseases of blood, interestingly Unani physicians have mentioned that in case of spleen enlargement, body and liver becomes weak therefore liver is unable to produce blood and simultaneously spleen absorb more amount of blood which leads to further shortage of blood. Fatigue, weakness, tiredness, fever these entire symptoms were described by ancient physicians under splenic diseases¹⁵ and same symptoms are mentioned in conventional medicine under caption of various hematological disorders.

Alteration in the blood whether in quantity or quality is one of the primary causes of morbid blood. Therefore, a test was included for effect of drugs on normal parameters of blood which aimed to determine whether the blood purifying drugs alter the normal parameters of blood and also to determine the underlying mechanism. For this purpose two groups of 12 rats (control and test) are tested to determine pre-treatment values. After the treatment for 21 days in test group blood samples are collected for the effects on BT, CT, RBC, Hb%, WBC, Platelet count, ESR, Osmotic fragility, Fibrinogen level, Glucose,

Table 1: Mechanism of action and therapeutic uses of *Musaffie dam* drugs

Actions	Mode/mechanism of action	Therapeutic uses
<i>Muhallil</i> (Resolvent)	Resolve thick and viscous humours	Inflammation of liver and spleen
<i>Mulattif</i> (Lenitive)	Liquefy thick and viscous humour	Hyperviscosity of blood due to phlegmatic humour in hyperlipidaemia and hyperglycemia
<i>Mujaffif</i> (Siccative)	Resolve viscous humours lying deep in the cavity and dry the exudates	Inflammation and ulcers
<i>Mu'arriq</i> (Diaphoretic)	Through perspiration remove waste material	Skin diseases and fever
<i>Mufattih</i> (Deobstruent)	Agitate the humoral matter lying deep in the cavity or orifice and open the passage to remove the obstruction	Obstruction in the liver and spleen, thrombosis
<i>Mudirr-i-Bawl</i> (Diuretic)	Increase viscosity of blood and remove waste material	Infection, fever, skin diseases
<i>Dafi'-i-Ta'affun</i> (Antiseptic)	Clear sepsis	Infections
<i>Mushil</i> (Purgative)	Expulsion of morbid humours by intestine	Diseases caused by altered temperament with involvement of morbid matter
<i>Dafi'-i-Humma</i> (Antipyretic)	Reduce body temperature during fever	Fever due to infection
<i>Muqawwi-i-Mi'da wa jigar</i> (Tonic to stomach & liver)	Strengthen and tone up the stomach and liver and improve its function	Stomach and liver diseases
<i>Muqawwi-i-Tihal</i> (Tonic to spleen)	Strengthen the spleen and improve its function	Diseases of spleen
<i>Mushtahi</i> (Appetizer)	Promote the desire for food	Loss of appetite due to stomach and liver diseases
<i>Hādim</i> (Digestive)	Improves digestion	Indigestion and weakness of stomach

Protein and Lipid concentration. In a study effects of *Safi* (Unani formulation of blood purifier drugs) and an allopathic hematinic Sangobion were observed on haematological and biochemical parameters in human volunteers. The increase in haemoglobin and erythrocytes was more prominent by *Safi*.¹⁸

Faqrudam (Anaemia) is denoted by various terms like 'Fasade Dam', 'Khūn ki tabahi' and 'Sooul Qiniya' in Unani literature.¹³ Improper function of liver affects the quality and quantity of blood. Blood purifying drugs maintain the specific composition of blood by their immunomodulator and hematopoietic properties.¹⁴ China root has beneficial role in *su ul qinya*¹⁴ and prevent from premature destruction of blood. Indian gooseberry.¹⁴⁻¹⁵ Chiretta¹⁹ and

a combination of Indian gooseberry and neem²⁰ showed haematinic efficacy in hemolytic anaemia. Sarsaparilla (*Smilax aristolochiaefolia*) was also found effective in benzene induced aplastic anaemia.⁹ The blood purifying drugs contain saponins,²¹ phenols,²² phenolic glycosides, alkaloids²³ vitamins²⁴ and minerals.²⁵ Triterpenic saponins stimulate the proliferation of lymphocytes for the production of interferon, hematopoietic growth factors and cytokines.²⁶ Alkaloids enhance the restoration of haematopoiesis.²⁷ The drugs which contain alkaloid, flavonoid, saponins have anti oxidant property so indirectly can be used in anaemia.²⁸ In the light above properties, two experimental models have been proposed viz. Phenylhydrazine

Table 2: Suitability and limitation of selected animal models for *Musaffie dam* drugs

Model for the diseases	Suitability	Limitation
Anaemia	Nutritional anaemia, hemolytic anaemia, anaemia due to chronic inflammation	Anaemia caused by congenital defect like thalassemia, sickle cell anaemia
Thrombocytopenia /purpura	Acquired caused by exposure to chemicals, bacterial and viral infections	Congenital
Polycythaemia	Primary polycythaemia	Secondary polycythaemia
Leukaemia	Chronic leukaemia	Acute Leukaemia
Thrombosis	Atherosclerosis deep vein thrombosis ecchymosis	Stroke
Infection and fever	Mild and chronic infection	Acute infection
Hyperlipidaemia and Blood Coagulation	Atherosclerosis Hypertension	Stroke, embolism, IHD
Hepatic and Stomach function	Jaundice, hepatitis, weakness of liver and stomach	Gastric ulcer , carcinoma of stomach and liver

induced hemolytic anaemia and benzene induced aplastic anaemia. Hemolytic anaemia is induced in Wistar rats by PHZ at 40 mg/kg orally for two days. Thereafter, the animals are treated with the test drug for 15 days.¹⁹ While aplastic anaemia is induced in male Swiss mice by 2 ml (1940 mg/kg) benzene subcutaneously. Three doses of benzene are administered weekly on alternate days until 10 doses are completed. After that, animal is treated with test drug for 15 days. The effect of test drug in both the models is evaluated by the estimation of RBC, WBC, Hb, hematocrit and LFT.⁹ Hemolytic anaemia is associated with intoxication with chemicals and drugs. PHZ is a strong oxidant agent. It shortens life span of RBC resulting in severe hemolytic anaemia.²⁹ Flavonoids are found in babchi,³⁰ chiretta,²¹ mundi,³¹ sandalwood,³² and Jujube³³ protect cells as powerful antioxidants which prevent or repair damage done to red cells by free radicals.³⁴ Tannins are present in sandalwood,³² Jujube,³⁵ and Indian gooseberry³⁶ inhibit the formation of superoxide ions and hydroxy radicals.^{37,38} On the other hand Immune dysfunction is believed to play an important role in aplastic anaemia.⁹ Indian gooseberry, china root and neem are well known “*rasayin*” having rejuvenating, immunomodulating and tonic properties.¹⁴ Glycoside and saponins significantly increase the proliferation abilities of bone marrow cell.³⁹ As these phytoconstituents are found in wild fig, chiretta,

mundi, and sandalwood.²¹ So blood purifying drugs may prove the haematinic potentials due to presence of these phytoconstituents.

Thrombocytopenia may result from intake of drug, chemicals, chronic liver disease and dengue hemorrhagic fever.⁴⁰ This condition can be correlated with “*riqqate dam*” (low viscosity of blood). As *riqqate dam* is one of the causes of *jiryannuddam* (haemorrhage) and *qatma* (hemorrhage beneath the skin).⁴¹ Low platelet count is most likely caused by ethanol causing portal hypertension and hypersplenism which resulted in thrombocytopenia.⁴² Liver damaged by ethanol can decrease production of thrombopoietin which decreases platelet production.⁴³ Thrombocytopenia is induced in rats by ethanol 3 g/ kg ip for seven days.⁴⁴ From 8th day the animals are treated with the test drug for further 14 days. The platelet count, bleeding and clotting time and histopathological analysis of the liver and spleen is done. The increase in bleeding time predisposes to prolonged hemorrhage and consequently excessive blood loss. This directly correlates with the decrease in the number of platelets in circulation. Clotting time measures the degree of activation of the coagulation pathways.⁴⁵ Blood purifying drugs are tonic to liver and spleen, restore the functions of these organs and normalize the blood composition. Jujube is used in *riqqate dam* (blood liquefaction). It normalizes excessive heat of blood and makes the blood less

viscous¹⁴ while Chiretta is useful in hemorrhage beneath the skin. In a study, *Carica papaya* leaves aqueous extract was investigated against thrombocytopenic rat model revealed significant increase in platelet count due to presence of saponins, tannins and alkaloids in aqueous extract, which act on the bone marrow, prevent its destruction and enhance its ability to produce platelets. Moreover, it can also prevent platelet destruction and thereby increase the life of the platelet in circulation.⁴⁶ Fortunately blood purifying drugs are abundant with these phytoconstituents. Hence the anti-thrombocytopenic effect of blood purifying drugs may be due to inhibition of platelet oxidation.⁴⁷

Thrombosis (sudda) is defined as homeostasis in the wrong place. Ibn Sina (980-1037 AD) has described that thrombosis form in lumens due to a foreign matter either due to increased consistency or viscosity or coagulated blood.⁴⁸ Deobstruent drugs possess detergent, demulcent and splitter properties,¹⁶ they liquefy the clot and agitate the humoral matter lying deep in the cavity or orifice and open the passage to remove the obstruction. Moreover, jujube, chob chini and wild fig are rich in saponins have antithrombotic and anti platelet action.⁴⁹ Furthermore, significant thrombolytic activity was demonstrated by ethanol extract and n-hexane fraction of wild fig.⁵⁰ On the basis of above properties an *in vitro* model for the preliminary screening of blood purifying drugs has been selected.⁵¹

The process of blood coagulation has a vital role in an organism's response to vascular injury and in thrombosis and cardiovascular diseases.⁵² Activated partial thromboplastin time (aPTT) and Prothrombin time (PT) are used to determine the coagulation factors.⁵³ A prolonged prothrombin time indicates a deficiency in factors V, VII and X, whereas a prolonged activated partial thromboplastin time represents a deficiency in factors VII, IX, XII, XIII and von Willebrand's factor.⁵⁴ Coagulation factors are synthesizing in the liver. If, liver will not function properly then synthesis of these factors will be disturbed and subsequently lead to coagulation disorder. Blood purifying drugs can act at this stage as they are tonic to liver and improve the power and function of liver thereby production of normal blood can be achieved.

An elevation in packed cell volume rather than a raised haemoglobin concentration, defines polycythaemia.⁵⁵ Polycythaemia is correlated with symptom attributed to hyper viscosity including somnolence, lethargy, poor concentration, and headache as described

in Unani literature in the symptoms of excessive blood.⁶ Increased blood viscosity, increased red and other blood cells and splenomegaly are essential diagnostic criteria of polycythaemia which can be correlated with hyperviscosity of blood, hyperemia and (*azme tihal*) splenomegaly respectively. Polycythaemia is induced in rats by inhalation of cobalt chloride (30mg/m³), 6hrs/day and 5 days a week for 13 weeks.⁵⁶ Increased blood viscosity in polycythaemia may be due to excessive black bile. Blood purifying drugs may be effective by purgation of black bile and normalize the function of spleen. Interestingly these drugs contain saponins²¹ can replace the use of aspirin in polycythaemia.

Abyazuddam (Leukaemia) is characterized by abnormal proliferation, differentiations and overproduction of WBC and their precursors⁵⁷ at which viscosity of blood is increased. Clinical features of leukaemia include weakness, lethargy, weight loss, fever, night sweats, and enlarged spleen and lymph nodes. This can be correlated with sign and symptom of "*azme tihāl*". Hippocrates quotes that when spleen enlarges body becomes weak, which is noticeable in leukaemia. Leukaemia is induced in rats by 0.2 mL of a 1:10 diluted benzene solution every 2 days for 3 consecutive weeks.⁵⁸ Blood purifying drugs by their alterative property may be effective in normalizing the quantity of these cells. Further these drugs have anti cancer,⁵⁹ anti oxidant⁶⁰ anti inflammatory^{61,62} and immuno modulator⁶⁰ activities. These drugs also rich in flavonoids and alkaloids.^{63,22} Alkaloids and flavonoids block the tyrosine phosphorylation,⁶⁴ induce caspase-3 activity and release the cytochrome C to activate the caspase-9,⁶⁵ and induce the expression of CD95 to induce apoptosis.⁶⁶ Immune function is disturbed in hematological diseases. Indian gooseberry, china root etc. strengthen the defensive mechanism and prevent the body from toxins. Tannin,³⁶ saponin,²¹ sterols²¹ and triterpene glycosides³² are found in drugs. It has been established that saponins have adjuvant effects on humoral cell mediated immunity,⁶⁷ Tannins,⁶⁸ sterols⁶⁹ and triterpene glycosides⁷⁰ are immunostimulant.

The coagulation system has been intended as a possible mechanism of thrombogenesis and atherosclerosis in patients with hyperlipidaemia. Hyperlipidaemia is a risk factor for ischemic heart disease, suggesting that hypercoagulability may perform a role in patients with hyperlipidaemia.⁷¹ Hence alterations in lipid levels influence thrombosis by modifying the activity of coagulation proteins, platelets and fibrinolytic

factors.⁷² Therefore, the model has been designed to evaluate the effects of blood purifying drugs on lipid profile and blood coagulation in hyperlipidaemia induced in rabbits by high cholesterol diet for 45 days. Thereafter animals are administered with the test drug orally for 30 days. Highly significant increase in thrombin time (TT) indicates deficiency of fibrinogen or inhibition of thrombin.⁷³ Significant decrease in cholesterol, triglyceride and LDL-C and at the same time increase in TT and fibrinogen time, indicating the probable decrease in the risk of atherosclerosis. Hence there are links between lipids and the haemostatic mechanisms which affect atherosclerotic, vasomotor and thrombotic components of ischemic heart disease.⁷⁴ So these models can be utilized for the screening of blood purifying drugs.

On the basis of above discussion it can be implicit that concept of morbid blood is a very wide in Unani system of medicine. The different properties of the blood purifying drugs such as alterative, anti-inflammatory, hematopoietic, tonic and demulcent comes from its bitter taste and hot and dry temperament. Demonstration of various effects such as tonic to stomach and liver, digestive, appetizer, diuretic, anti septic, antipyretic along with its research reports may give rise to total effects in amelioration of hematological disorders. Since blood purifying drugs possess a wide range of pharmacological effect, therefore it can be said that it may prove its

effectiveness by evolving a holistic paradigm and involving its numerous actions. Saponins, flavonoids, alkaloids, vitamins, minerals, tannins, glycosides, amino acids, steroids, triterpenoids, etc. present in the drug further corroborates the proposition that the blood purifying drugs may produce effect through diverse mechanism complementing each other.

Conclusion

It can be concluded therefore, that the effect of blood purification may be related to all the above reported actions and chemical constituents of the drugs which may act to ameliorate the morbid blood. So this study may serve as a tool for screening the blood purifying drug which is one of the broadest terms for the effect of drugs in disorders of blood.

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Authors' Contribution:

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