## Kinetic Synergism in Herbal Medicine: Traditional Medicines from a Modern Scientific Perspective

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Kinetic synergism in herbal medicine: traditional preparations in terms of modern scientific understanding

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## RESUME

The analysis of the formulation of the "Urolesan" preparation authorized for medical use in the Soviet Union 30 years ago, in terms of modern ideas about biologically active substances of natural origin and compatibility of ingredients was done. It is shown that combination of herbs demonstrates the principle of kinetic synergism of components, when one-way types of pharmacotherapeutic action are realized in the body by various mechanisms using biologically active substances of diverse structure. This principle, along with natural origin and quality of phytopharmaceutical remedy determines the reliability of therapy, including the period of establishing an accurate diagnosis, and the high demand for the product under research both by specialists and the public.

Keywords: evidence-based herbal medicine, phytokinetic synergy, kinetic synergy in herbal medicine, biologically active substances, kidney stones, inflammatory diseases of the kidneys and bladder.

## SUMMARY

The analysis of the formulation of the drug "Urolesan", approved for medical use on the territory of the USSR more than 30 years ago, from the point of view of modern ideas about biologically active substances of natural origin and the compatibility of the incoming ingredients, has been carried out. It is shown that the composition of the combined herbal preparation clearly illustrates the principle of kinetic synergism of the components, when unidirectional types of pharmacotherapeutic action are reliably implemented in the body by various mechanisms using biologically active substances of various structures. The implementation of this principle, along with the natural origin and standard quality of the investigated OTC phytopharmaceutical agent, determines the reliability of therapy, including during the period of establishing an accurate diagnosis, and the high demand for the investigated drug by specialists.

Key words: evidence-based herbal medicine, phytokinetic synergy, kinetic synergism in herbal medicine, biologicallyactive substances, urolithiasis, inflammatory diseases of the kidneys and bladder.

# Introduction

The modern terminological unit "phytopharmaceutical" means a standardized drug that either exclusively or predominantly consists of biologically active substances (BAS) or substances of plant origin, as well as from medicinal plant materials or galenic extracts from it [15, 16, 18, 33] ... Registration of modern phytopharmaceuticals today is carried out on a general basis with synthetic drugs and implies the existence of an evidence base for their effectiveness (preclinical and clinical studies) and safety (acute and chronic toxicity, teratogenicity, mutagenicity, etc.) [16, 33, 34]. The same rules apply to drugs that undergo periodic re-registration after 5 years from the date of their registration.

Therefore, it is very interesting to analyze the rationality of traditional formulations of official multicomponent herbal preparations of various pharmacotherapeutic groups, which were approved for medical use more than a third of a century ago. One of the most popular drugs known on the domestic market for more than 30 years is "Urolesan" [ATC: G04BC Drugs for the treatment of nephrourolithiasis].

The demand for drugs on the part of specialists and the population, as a rule, is due to a number of factors, in particular, efficiency, affordability, natural origin, standard quality and even adherence to the rule known in phytotherapy: "treat with the area", that is, drugs based on domestic medicinal plants ... Urolesan (Urolesanum), the recipe of which has roots in domestic traditional and folk medicine, was developed and registered in the 80s of the last century, passed the necessary re-registration procedures and today is still perceived by many experts as a reliable and safe urolithic and uroseptic, and sales it grows from year to year. In the list of top 10 brands of medicines (drugs) in terms of pharmacy sales in its competitive group G04B in monetary terms,

In accordance with the approved Instructions for Use, Urolesan has antiseptic properties, increases urine output, acidifies urine, increases the excretion of urea and chlorides, enhances bile formation and bile secretion, and improves hepatic blood flow. It is prescribed for adults and children over 7 years of age in the treatment of urinary and cholelithiasis, urinary diathesis, acute and subacute calculous pyelonephritis and chronic cholecystis, biliary dyskinesia. According to the NO "PANT", the most popular official indications for the use of the drug are various forms of urolithiasis, as well as acute and chronic pyelonephritis [16, 17].

Therefore, in this work, we were of particular interest to substantiate the effectiveness of the drug when used as a basic therapy or as part of a complex treatment of urolithiasis (Urolithiasis), as well as acute and chronic infections of the urinary bladder and kidneys.

The aim of the study is to analyze the formulation of the drug "Urolesan" from the standpoint of the principle of kinetic synergy and modernideas about biologically active substances, which determine a wide range of pharmacotherapeutic action of standardized herbal preparations.

# 1. The problem of the Whole and the Particular in herbal medicine

Following the general enthusiasm for the process of isolating the active principle in the form of crystalline compounds from raw materials of natural origin in the 60s of the XX century, the point of view about the advisability of returning to galenic preparations preserving the native (natural) natural complex of biologically active substances [13, 16, 19, 38]. Already in 1979, the president and founder of the French National Institute of Herbal Medicine in Paris, P. Belaiche, categorically stated that "the desire to treat with a single component, discarding the whole plant or neglecting complex herbal preparations, is definitely a serious mistake" [35].

He also owns the following statement, which led in the late 90s to a number of successful clinical trials of herbal preparations in accordance with the principles of the GCP: "Some specialists, due to lack of information, still have a desire to conclude the therapeutic truth in one formula at any cost ... However, life develops thanks to a variety of enzymatic reactions. A pathological state is created in the likeness of a physiological state, that is, a complex, polymorphic, multidirectional. It is illogical to show that the action of a single pure molecule is sufficient to regulate a multitude of perturbed reactions. A pathological condition cannot be reduced or eliminated only by a chemical agent, since it is not monomorphic "[35].

In 1991, the results of scientific studies carried out in the PRC were published, which reliably showed that "due to mutual restraint or reinforcement in the action of each other, medicinal plants (or other natural ingredients) can fully manifest their effect, limiting their own toxicity [13, 37] ... This explains the fact that almost all traditional medical schools have used multicomponent drugs of natural origin since ancient times [13, 16]. 10 years earlier, Paul Belesch first proposed to designate the described phenomenon by the term "phytokinetic synergy". This irreplaceable component of the treatment process meant the symbiotic action of the constituent elements of the same plant or different plants [35].

2. Kinetic synergism in herbal medicine

One of the known ways to increase the efficiency of any multicomponent system (in this case, a multicomponent herbal medicine) is the use of compositions of various ingredients that exhibit a synergistic effect. Synergy, or synergy (Greek συνεργία, from Greek syn - together + ergos - acting, action) is understood as the summing effect of the interaction of two or more factors, characterized by the fact that their action significantly exceeds the effect of each individual component in the form of their simple sum ...

There are three types of implementation of the mechanisms of synergism of ingredients: kinetic (absence of any interaction between the components of the mixture), chemical (chemical interaction of ingredients or products of their transformation) and physical (due to the influence of physical factors or physical interaction of components).

Our analysis of the formulations of traditional drugs and the arsenal of modern phytopharmaceuticals approved for medical use on the territory of the Russian Federation [7, 15] made it possible to establish the presence of a number of drugs that duplicate the main types of action of each other and to reveal the following patterns.

The number of ingredients in individual recipes varies depending on the national and personal characteristics of traditional herbalists [1, 9, 13, 22-26, 36, 39], and in finished herbal preparations - depending on the dosage form and the country of manufacture [13, 14, 40, 41].

The national peculiarities of the selection of formulations when discussing the issue of kinetic synergy in herbal medicine can most clearly be traced in herbal preparations of European and Eastern countries [14].

Medicines of traditional European schools and modern herbal remedies, as a rule, are low-component, are built according to a certain algorithm (1-2 main ingredients, 1-2 - enhancing the effect of the main, one flavoring agent, the action of which, as a rule, coincides with the main one, and one filler giving the drug has an attractive appearance, which also acts unidirectionally with the main ingredient) [5, 16].

Oriental recipes are based on local raw materials, take into account the national characteristics of the patient and the traditions of the local school of TM. At the same time, multicomponent drugs with up to 50 ingredients are still welcome [13, 30–32]. Grinevich M.A. [8] explained this by the desire to complicate the natural complex in order to enrich it with information content in accordance with the theory of structural information and modern scientific ideas about the information content of food and medicinal plants [2-4]. The following explanation is more understandable from the point of view of modern physiologists and clinicians. Since in the pathogenesis of most chronic diseases a significant place is occupied by disorders in the "central regulatory triangle": the nervous, immune and endocrine systems,

Another feature of oriental recipes is the duplication in one recipe of a certain type of action by several components working according to different mechanisms [8, 11–13, 30–32]. In one of the studies, for example, as a result of the analysis of more than 1000 oriental formulations (Japanese, Korean, Chinese medicines), 422 cases of duplication of the same action were found, and the tonic was duplicated 91 times, diuretic - 63, antitoxic - 46, expectorant - 44, antispasmodic - 27 times [8, 13].

In other words, unlike European schools, oriental recipes demonstrate the predominant inclusion in them of agents with a general effect on the body (up to 60% of ingredients), a smaller part is symptomatic and very small is of local action. And the most commonly used types of general action are just antitoxic, anti-inflammatory and tonic [13].

3. Analysis of the rationality of the composition of the drug "Urolesan" from the point of view of modern ideas about biologically active substances

After nonspecific inflammatory diseases of the kidneys and urinary tract, urolithiasis (Urolithiasis) in urological pathology ranks second in prevalence [20, 28]. The incidence of KSD in the world ranges from 0.5 to 5.3%. At the end of the last century, it was reliably shown that in some countries and areas this disease is endemic, which, according to most leading urologists, is due to the peculiarities of climatic factors, the composition of water, and the nature of nutrition [6, 20, 21].

Treatment of urolithiasis consists in removing stones, eliminating the cause that caused their formation, and the associated inflammatory phenomena in the urinary organs. Urolithiasis is, first of all, a surgical disease, since in order to get rid of patients from stones, it is often necessary to resort to one or another surgical method of their removal. The exception is stones consisting of uric acid salts urates, which are subjected to more or less successful dissolution with citrate mixtures (uralite U, blemaren, etc.). Therapy with citrate mixtures for 2-3 months often leads to the complete dissolution of such stones. For stones of a different composition, stone-dissolving therapy is ineffective. The success of minimally invasive therapeutic technologies, such as: extracorporeal lithotripsy, causes a decrease in interest in research in the field of drug therapy and prevention of urolithiasis, which may be a likely reason for the increase in morbidity. At the same time, the removal of a stone or its independent discharge from the urinary tract does not relieve patients of the possibility of recurrence of this disease, since the main processes leading to the formation of stones, as a rule, are not eliminated. Therefore, the role of various conservative (medicines, physiotherapy, balneo and phytotherapy) methods of treating this disease is significantly increasing, which are mainly aimed at preventing relapse. since the main processes leading to the formation of stones, as a rule, are not eliminated. Therefore, the role of various conservative (medicines, physiotherapy, balneo and phytotherapy) methods of treating this disease is significantly increasing, which are motel minated. Therefore, the role of various conservative (medicines, physiotherapy, balneo and phytotherapy) methods of treating this disease is significantly increasing, which are mating at preventing relapse.

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For polyphenols, and in particular flavonoids (including anthocyanins, catechins), pronounced anti-inflammatory, capillary-strengthening, antioxidant and antihypoxant types of action are proven. Due to the contribution to the total effect of each group of biologically active substances,

Urolesan has a pronounced anti-inflammatory effect, promotes the elimination of small calculi from the kidneys, urinary and gall bladders, and even prevents their formation due to the competitive relationship of silicon compounds coming from plants and calcium [13, 14, 17, 27]. To reduce crystal formation, growth and aggregation of calcium oxalate and calcium phosphate crystals in urine, vitamins are also extremely important, in particular tocopherols [34], which enter the body with the fatty acid fraction and the plant macro-microelement component of the Urolesan preparation. Pyridoxine reduces the synthesis of oxalic acid and stimulates the processes of its neutralization in the liver [34].

Free amino acids of medicinal plants (they participate in biosynthesis, transport and increase the bioavailability of other groups of biologically active substances) play a huge role in the treatment of KSD and inflammatory diseases of the kidneys and urinary bladder [14, 16], incl. methionine and glutamic acid, which are included in the form of finished preparations (of synthetic origin) even in standard therapy for phosphate-type stone formation [34]. Due to the presence of terpenoids and polyphenols of a flavonoid nature, the drug has a mild sedative and antispasmodic effect, which is

very important in the discharge of calculi.

#### 4. Method of administration and dosage

Urolesan is used orally before meals, 8-10 drops on a piece of sugar under the tongue 3 times a day. Duration of admission is 5-30 days. Repeated courses are possible if necessary. With renal and hepatic colic, a single dose can be increased to 15–20 drops. Doses for children aged 7-14 years - 5-6 drops (for sugar) 3 times a day. Contraindications: hypersensitivity to the components of the drug, gastritis (except for gastritis with secretory insufficiency), peptic ulcer of the stomach and duodenum. In case of an overdose, nausea, dizziness are possible; treatment: plentiful warm drink, rest, intake of activated charcoal, appointment of atropine sulfate (0.0005-0.001 g). With increased sensitivity to the drug, slight dizziness, nausea, vomiting, dyspeptic symptoms, sometimes allergic reactions in the form of a rash, itching, hives. In general, Urolesan is well tolerated, which allows it to be used from the age of seven.

## The discussion of the results

One of the factors that determine the demand for the drug is its effectiveness and reliability, including with an unclear diagnosis or the impossibility of clearly identifying the substrate of the disease at one stage or another of the development of the pathological process.

From table. 1 shows that the composition of the drug Urolesan more than 30 years ago was selected taking into account the basic rules of classical herbal medicine [19] and demonstrates an example of a complex effect on various links of the pathological process and on the body as a whole. It should be recalled here that one of the postulates of any therapeutic and prophylactic process in phytotherapy is the effect not only on the affected organ, but also on the associated systems of the body [16, 19]. Analysis of the table. 1 also made it possible to establish that the reliability of the drug increases due to the implementation of one of the most frequently used principles of Eastern herbal medicine - duplication of unidirectional types of activity using ingredients of different chemical structures and different mechanisms of their action [13].

The investigated drug is a classic example of the implementation of the principles of kinetic synergism and demonstrates repeatedly duplicated various types and mechanisms of action of the incoming ingredients. In other words, the formulation of the investigated drug can be confidently attributed to the classic phytotherapy recipes, tested by more than one generation of specialists.

# Conclusion

Thus, the information and analytical study carried out made it possible to establish that the composition of the finished medicinal product (combined herbal preparation) "Urolesan" clearly demonstrates the principle of kinetic synergy of components known in phytotherapy, when unidirectional types of pharmacotherapeutic action are reliably implemented in the body by various mechanisms using biologically active substances of various structures. The implementation of this principle, along with the natural origin and standard quality of the investigated OTC phytopharmaceutical, determines the reliability of therapy, including during the period of establishing an accurate diagnosis, and the demand for the investigated drug by both specialists and the public.

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# Types of pharmacotherapeutic action of biologically active substances of plant origin included in the drug Urolesan

Haa	вание		Применение рас-		
Компонент препарата Уролесан, на 100 г	Производящее рас-		тения в официаль-	БАВ, переходящие из растения в препарат	Фармако-тера центическое действие БАВ
	тение (Сем	енство)	практике		
Масло постовое, Oleum Abietis (Abietis Balsamum), 8 г	Пихта си- бирская	A bies sibirica Ledeb.	Источник эфирно- го пих тового масла и жизницы. Сырье	<ol> <li>Терпенонды (эфирные масла) с преобладанием бориялацетата – ок. 50–60 %; сопутствующие тер- лены – борнеол, камфен, альфа- и бета-тинен</li> </ol>	Противовоспалительное, раздражающее, выраженное анти- септическое, регенерирующее
		and a strategy of the state of the	для получения масляных раство- ров и эмульсий	2. Жирорастворимые витамины	В сочетании с соединениями кремния, магния, калия пре- питствуют кристалпообразованию, росту и агрегации кри- сталлов оксалата и фосфата кальция.
Маслю мяты перечной, Oleum <b>Menthae piperi</b> - tae, 2 г	Мята перечная	Mentha piperita L	Седативно- спазмолитическое, желтеговное; источник эфирного мятного масла	<ol> <li>Терпеноиды (эфирные ма сла), основные компо- ненты ментса (50–50 %), ментся (10–20 %), ментс- фуран, эфиры ментсла с укусуской и козовалерияно- вой кислотами (5–20%). Кроме того, содержится в свободном виде изовалериановая инслота.</li> </ol>	Выраженное спазмолитическое, седа тивное, противовоспа- лительное, автиселтическое, выраженное анальтетическое, дегиме раздражающее, диуретическое и желтегонное
				<ol> <li>Макро- и минроэлементы, в том числе в форме органических и минеральных солей</li> </ol>	Коферменты ферментов. Источники защитных коллондов, пре питетаующих образованию, росту и агрегации оксалатов и фосфатов калыция в моче.
Масло касторовое (масло семян клеще- вивы обытнов епной), Oleum Ricini, 11 г	Клещеви- на обыкно- венна я	Ricinus communis L	Источник жирного масла, обладающе- го слабительным действием	<ol> <li>Жирное масло, состоящее на 85-87 % из одно- нислотного триглицерица рицинолевой кислоты (12-тидроксилоненновая кислота); оленновая к-та (ок. 9%), ливилевая к-та (ок. 3%)</li> </ol>	Слабительное (масло расщепляется лизназой в товком импечиние с образованием рицинолемой всты, которая вы- ныма егразиражение рецепторов импечника, приводящее к усилению перистальтики)
				2. Жирорастворимые витамины	В сочетании с соединениями кремкия, магния, калыя пре- питствуют кристаллообразованию, росту и агрегации кри- сталлов оксалата и фюфата кальция
Спиртовой экстракт овилимораль и диола, Extractum fructibus Dauci carotae, 23r	Морковь дикая	Daucus carota (L.) Thell	Спазмолятиче- ское, обладающее диурстическами, бактерицидаь- ми, противовос- политераными свойствами	<ol> <li>Терпенонды (эфирные масла) – 1,4–2,9 % с пре- обладанием гераниола (до 60 %), цитраль, альфа- пинен, лимонен, газрон</li> </ol>	Бактерицидное, спазмолитическое
				<ol> <li>Кумарины (0,8%) – кумарин, умбеллиферон, эскулетин, сконолетин, а также фурокумарины (ксавтотоксия, пеуцедания)</li> </ol>	Спазамолитическое, способствующее отхождению камней из мочеточныко в
				3. Сопутствующие в-ва: – жорное масло (11–50 %), – флав помоды (проявлающые дотеолина, диосмети- на, кверцетива, апигенена), – ма кро- и микроолементы, – озободине в оминокислоты, в т.ч. метиония и глута- меновая кислота.	Противовоспалительное, защищающее от повреждающего действия раздражающих вещесть, актиюкаудаятное. В сочета вис с соедисензими сремника, магния, казлия, пре- пятствуют кристадисобразованно, росту и агрегации кри- сталлов оксалата и фоофата нальния. Аминовислюты оксазывают метаболическое действие, по- выпшот биодосту пиость других групп БАВ. Метноныя и гаутаминовая изслота обладают выдаженной активностью при фосфатном типе камнеобразования.
Hare	ame		11		
Сомпонент препарата Уролесая, ва 100 г		Применение рас- тепия в официаль- ной медицинской практике	БАВ, переходящие из растения в препарат	Фармако- теранев тическое действие БАВ	
Спиртовой разрето ит	YNOT	Натинское	Солтананованы	1 Tennegoums (adapting the cred) = 1=2% any open-	Constanting communes (mathematication we themptyce)
Cnupronoß buzrpar numer xwerk, Extra- tum Humuh lupuh, 32,995 r	Амель обытно- ренный	no-lupuhis L.	Седативное при неврастении, бессовнице, не- враллии. Противо- казенные, астро- геноподобное. Противокогда ли- тель ное (особенно при иосплаятель- ных забодеваниях почек, мочевого и желчиого пузыри), при заболеваниях	<ol> <li>Герненовда (одвръва масла) - Г. 3 ж. одвержа- ще моно- и секвитериства – менден, фаркезен, альфа-кариофиялен (гумулен), бета-кариофиялен</li> <li>Горечи – 11–21 % – производные флороглопидов идр.</li> </ol>	Седативное, сомловаю (диу резическое, желчеговное), вяльтьетическое. Седативное действие обусловлено гл.о. 2-метил-3-бутен- 2-одом (пов вялотии с немещими препаратом на основе 3-метил-пентин-сма-3), образующегося в организме из горыких кислот в результате биогрансформации
				3. Фенольные соединения – флавоновды – кемп- ферол, кверцетик, мирицетик и их тикозида (изокверцетрик, рутик, астрагалик, кверцетрик), антоцовновина (цизвидия, дельфиниция), (+)-ка- техик, (-)-отвка техни; кумерины, фенолка рбоновые киклоты (хлорогено- вал, кофейнал, феруловал)	Противовоспалительное, в ротивоязвенное, капилля роукре- цивощее, автиок сидантное, а нтигипоксавтное
			лите и заболевани- ях суставов. Диуретическое. Препараты из	<ol> <li>Макро- и микрохлементы, в том числе в форме органических и миверальных солей.</li> </ol>	Коферменты ферментов. Источники защитных коллондов, препятствующих образованно, росту и а грегации оксалатов и фосфатов калыция в моте.
			плящек хмеля тра- диционно приме- внот при лечения хроничесного и острого пледовеф- рита, в гачестве божеутоляющего при почечно- каменной божеми и циститах.	<ol> <li>Сопутетнующие вещества: интамины – группы В, токоферолы, аскорбиновая к-га, встрогенные гормины, свободные вминовислоты</li> </ol>	Капилияроукрепияющее, анальтетическое, противовоспа- лягчелыкое, антиоксидантное. Токоферолыкое, антиоксидантное. Токоферолы в сочетавки с соединеннями кремпям, магния, калия препятствуют кристаллособразованию, росту и агрега- цои криста лало в оксалата и фосфате на льдия. Пиридожени способствует уменьшеняно синтеза щавеле- вой кислоты и стиму алции процессов ее нейтрализации в печеня. Аминописаюты окалы вакт метаболическое действие, по- вышают биодоступность других групп БАВ. Метиовия и гаутаминован виспота обладают выразменной активностью при фосфатном типе камисобразования.
Спартовой экстракт травы душицы, <b>Ex trac</b> - tum Origani vulgaris, 23 r	Ду шица обыкно- венная	Origanum vulgare L	Отхаркивающее, потогонное, проти- вовоспалительное, седативное	<ol> <li>Терпенонды (эфирты е масла), основными компонентами которых являются ароматические соединения (монотерпеновые фенолы) – тимол и караварол – до 44 %. В нефевольную фразцюо эфиркого масла входит моно- и сесявитерпены и их кислородные производныеб п-цимол, геранила це- тат (до 5%), злъфа-такнен, марцен и др.</li> </ol>	Противовоспалительное, раздражающее, выраженное авти- септическое, седативно-спазмолитическое, диуретическое
1			1		
				<ol> <li>Полифенольные соединевия: флавоновды (гливозиды лотеолика, апитеника, двосметика), дубильные вещества (до 8 % в сырье)</li> </ol>	Противовоспалительное, седатявно-спазмолитическое, антиоксидантное, автигипоксантное, Р-в итам инное

Kiseleva, T.L. Kinetic synergism in phytotherapy: Traditional drugs from the point of view of modern scientific concepts / T.L. Kiseleva // Traditional medicine. - 2011. - No. 2 (25). - S.50-57.

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