Of Devils and Angels
- Synergistic Effects –

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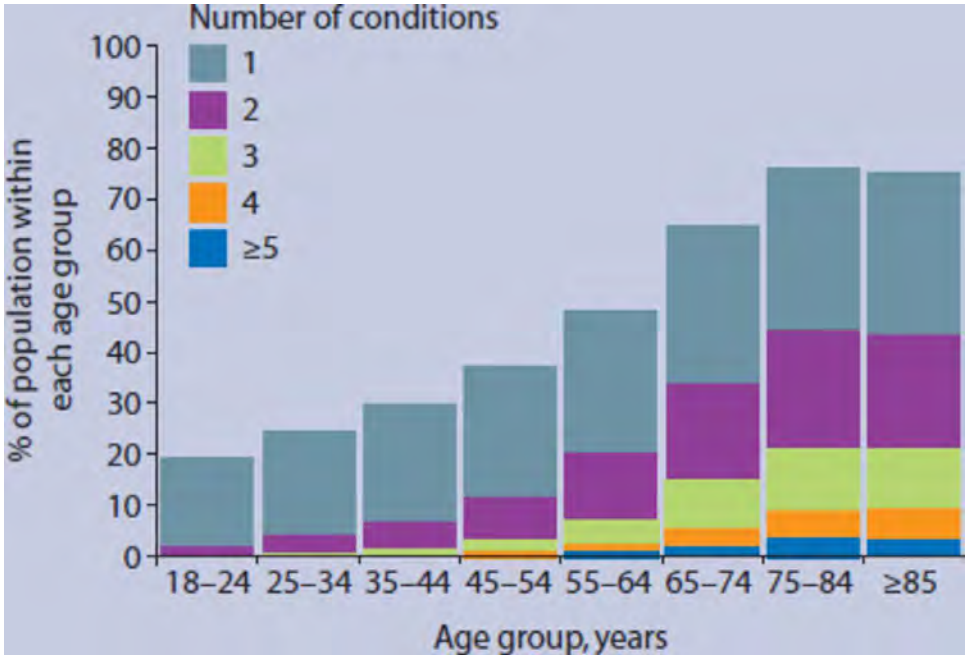
The Book of Revelation describes a war in heaven between “angels” led by the archangel Michael against those led by "the devil“ (Luzifer), who are defeated and thrown down to the earth. **Therefore, in principle, the “devil” must have been an “angel” in advance.**

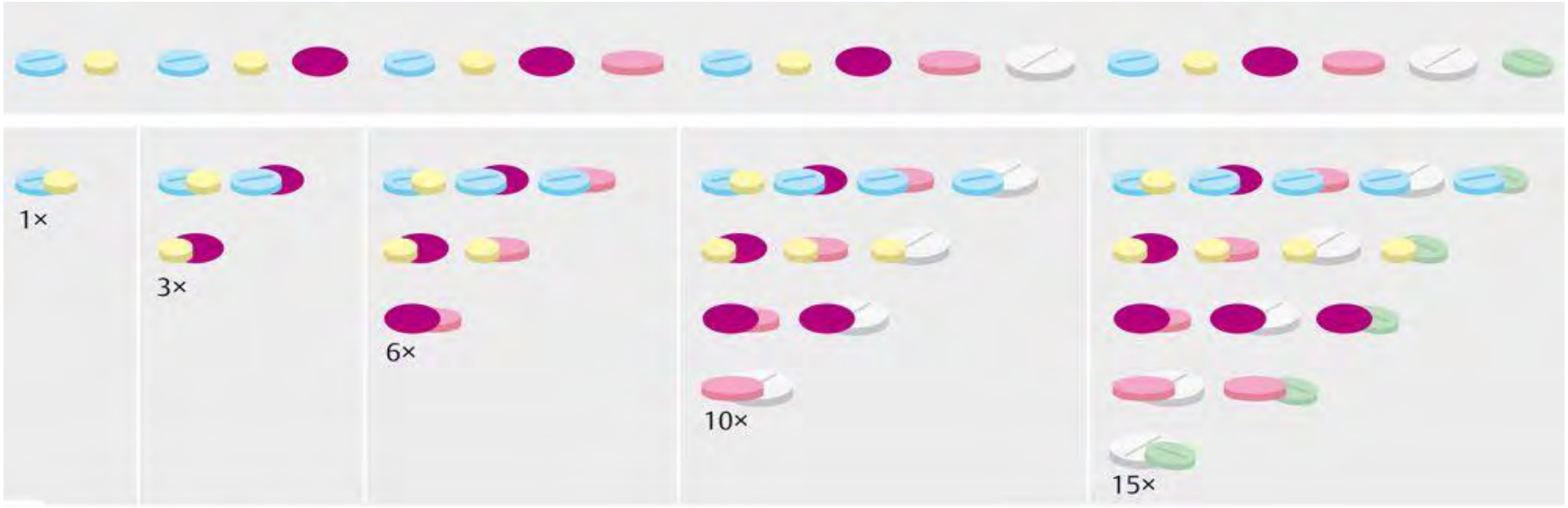
Comparing this picture with the treatment of diseases, the “devil” can be regarded as the negative effects of medicines in in combination treatment. If the medicine in given as “monotherapy” it is an “angel”, if it is applied with a (wrong) combination-partner, it can turn out to be a “devil”. The classical main task of pharmacovigilance is to identify such “devils” and avoid them. Textbooks are full of always the same negative interactions, but due to lack of ethic to conduct RTCs, the well-known examples a limited and are mainly discovered by chance. **The result over years, common knowledge of classical pharmacology is: “Avoid Combination!”**

Drug Regulatory Affairs

The ageing society brings up more and more “multi-morbidity” patients (means needing polypharmacy) where the influences of different drugs to each other are mainly unknown but the combination is unavoidable, caused by the severity of the diseases.



I know a nearly 100-year old woman, who has to take 14 different medicines each day.



A major argument against combination products was, however, that different ingredients could result in different blood levels or durations of action, e.g. the synchronization of the bioavailability of the substances. However, this is only convincing, if the mode of action is needed simultaneously, not, if there are different targets (with in the end similar outcome) and/or an overlapping longer period of “steady state” for both.

But is this REALLY the full truth?

For example some common “state of the art” therapies with chemically defined substances:

There are serious diseases, from which since a long time, is known that they can't sufficiently be influenced (or cured) with one drug alone, e.g. tuberculosis (Isoniazid, Rifampicin, Ethambutol; today plus Pyrazinamide).

WHO Treatment Guidelines for Standard Regimens for New TB Patients	
Intensive phase treatment*	**Continuation phase**
2 months of HRZE* (H) Isoniazid (R) Rifampicin (Z) Pyrazinamide (E) Ethambutol	4 months of HR (H) Isoniazid (R) Rifampicin
* WHO no longer recommends omission of ethambutol during the intensive phase of treatment for patients with non-cavitary, smear-negative pulmonary TB or extrapulmonary TB who are known to be HIV-negative. In tuberculous meningitis, ethambutol should be replaced by streptomycin.	

Source: heathlingardhsc4233.blogspot.com

And in the last years the disease needing combination-therapy increased: E.g. Human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) ect.

SVR Responses with GT 1 HCV-HIV Coinfection and HCV Monoinfection

Regimen (12 weeks)	Genotype 1			
	HIV-HCV Coinfected		HCV Monoinfected	
	Study	SVR	Study	SVR
Daclatasvir + Sofosbuvir	ALLY-2	**97%**	AI444040	**100%**
Ledipasvir-Sofosbuvir	ION-4	**96%**	ION-1	**99%**
Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir	TURQUOISE-I (+ Ribavirin)	**94%**	PEARL-III, IV (+/- Ribavirin)	**96%**
Elbasvir-Grazoprevir	C-EDGE Coinfection	**95%**	C-EDGE TN	**95%**

Source: hepatitisc.uw.edu

And in the last years the diseases requiring combination-therapy increased: E.g. Multi class combination products for “acquired immune deficiency syndrome” (HIV/AIDS) ect.

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Agent	Approved	Dose	frequency
Atripla: (efavirenz/ emtricitabine / tenofovir disoproxil fumarate)	12-July-06	600mg/ 200mg / 300mg	OD (E S)
Complera : (emtricitabine/ rilpivirine/ tenofovir disoproxil fumarate)	10-August-11	200mg/ 25mg / 300mg	OD (W M)
Stribild : (elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil fumarate)	27-August-12	150mg/ 150mg/ 200mg / 300mg	OD (W M)

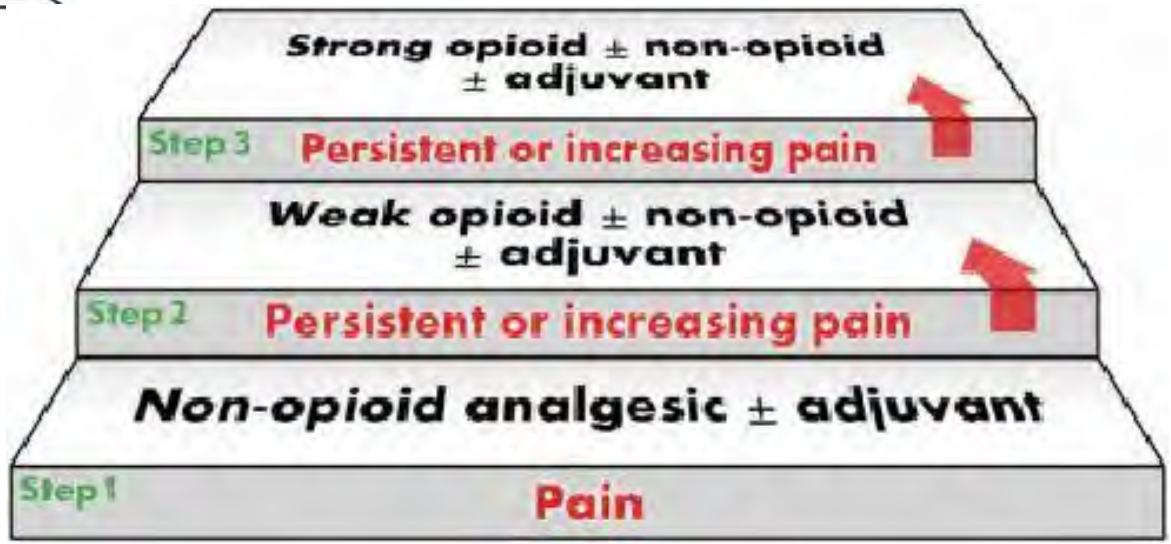
Source:http://image.slidesharecdn.com/hiv-151111110816-lva1-app6892/95/hiv-and-aids-treatment-2015-35-638.jpg?cb=1447241487

or helicobacter pylori eradication (standard first-line therapy is a one-week "triple therapy" consisting of proton pump inhibitors as omeprazole and the antibiotics clarithromycin and amoxicillin).

Drug	Dosing	Duration (d)	Eradication Rates
PPI, Clarithromycin, Amoxicillin	Standard dose BID, 500 mg BID, 1000 mg BID	10-14	70-85%
PPI, Clarithromycin, Metronidazole	Standard dose BID, 500 mg BID, 500 mg BID	10-14	70-85%
Bismuth subsalicylate, Metronidazole, Tetracycline, AND Ranitidine OR PPI	525 mg QID, 250 mg QID, 500 mg QID, 150 BID standard dose, QD to BID	10-14	75-90%
PPI, Amoxicillin; THEN PPI, Clarithromycin BID, Tinidazole	Standard dose 1 g BID; Standard dose BID, 500 mg 500 mg BID	5 5	>90%

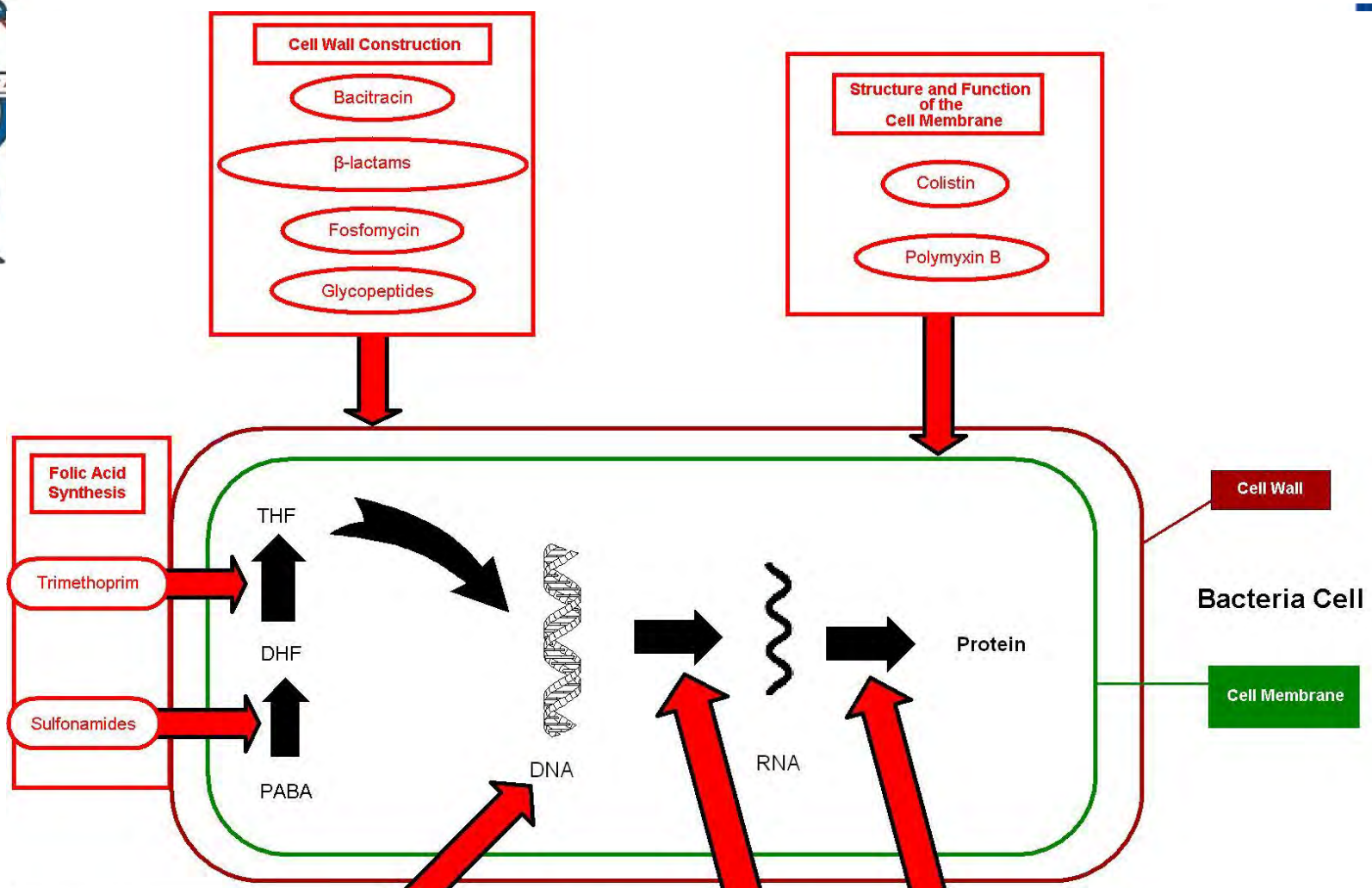
Source: img.medscape.com/pi/features/slideshow-slide/peptic-ulcers/fig12.jpg

I think in the past we have often overseen, that the “devil-angel” picture can also be used for the positive effects on interaction. Even in chemically defined therapy it is well known, that there are positive examples of combination therapy.



I want only to focus on analgesics with the result “pain-relief”, but with different point of action in the human body like NSAR and opioids. They differ in their influence on the perception of pain because they have different targets, e.g. peripheral and centrally. E.g. by combination of Morphine and Ibuprofen you can increase the allover pain-relief of severe pain and/or reduce the side effects of the single substances. So the combination of these DIFFERENT points of action is hope to many pain-suffering patients.

For example, if it would be possible to attack a germ at the same time with all different modes of action (e.g. cell-wall, -membrane, RNA, DNA etc.) it would be possible to eradicate the germ with lower dose of the single substances, means less side effects and eradication should result in less resistance. However, up to today this seems to bee only a dream. But is this REALLY the full truth?



Source: Wikipedia

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In natural plants there exist lots of examples, exactly using this prinziple. Mainly acting against „predators“ of the plant.

Very often we have overseen this effect, because the sustances are acting „mild to moderate“ and, since ancient times in drug research, we are looking for „strong acting“ compounds like morphine.

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Since a very long time humans are using “self-synergistic” therapeutic agents, the natural occurring plants and pharmaceuticals therefrom. These were the first attempts for treatment in history, even used by animals e.g. elephants, apes and even birds.

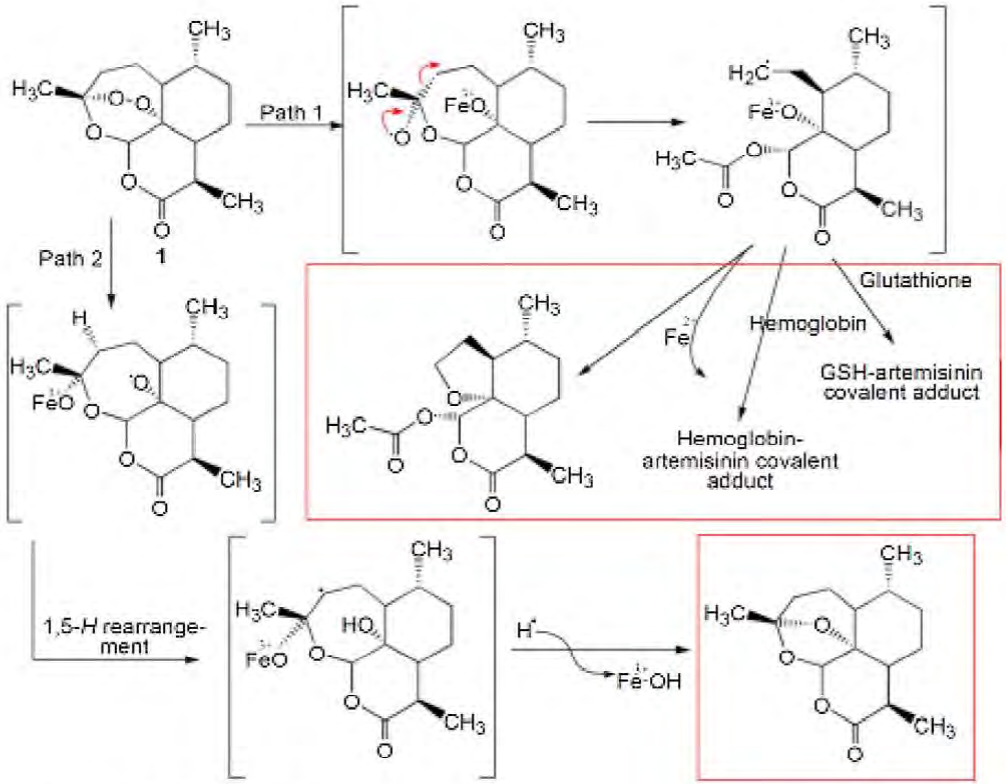
On smartest are well apes, the search for specific plants to cure certain ailments and diseases. If chimpanzees have intestinal worms, then they are looking for the leaves of Aspilia plant, a kind of Wild Sunflower. They are really hairy until prickly and bitter taste. Normally, the monkeys would not eat. But sick animals pick these leaves, fold it with his lips and swallow them down without chewing. They pass almost undigested from the stomach into the intestine. Exactly then remain the worms in the hairs of leaves hanging and transported them to the outside.

This observation was made by the University in Kyoto Professor Michael Huffman, who has long studied chimpanzees in Tanzania.

Plants “protects” vulnerable substances within a matrix, which stabilizes them e.g. by reductones, makes them easier soluble. Therefore, the plans may use since decades the principle of synergy to protect themselves in the evolutionary process to survive.

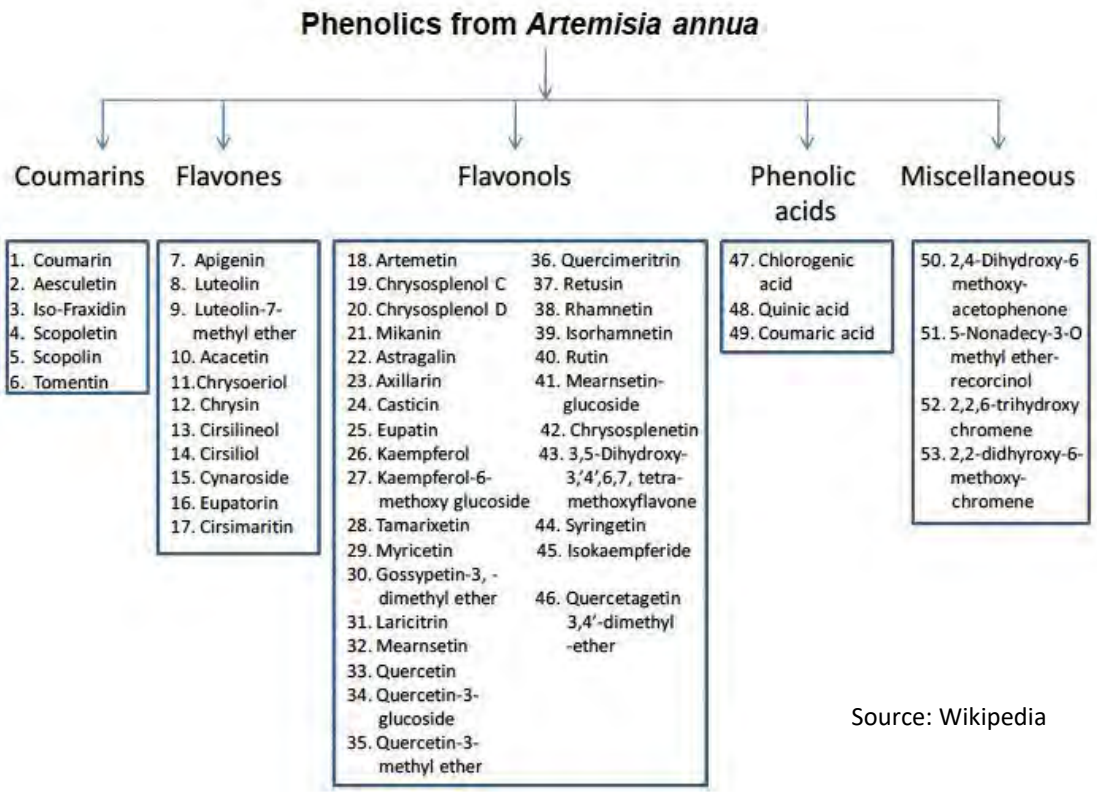
For the discovery of Artemisia annua as an effective remedy against malaria Tu Youyou (born 30 December 1930) was awarded the 2015 Nobel Prize for Medicine. Tu is the first Chinese Nobel laureate in physiology or medicine and the first citizen of the People's Republic of China to receive the Nobel Prize in natural sciences.

A good example for that is Artemisia annua, we use in the therapy of malaria. The proposed mechanism of action of artemisinin involves cleavage of endoperoxide bridges by iron, producing free radicals, which damage biological macromolecules causing oxidative stress in the cells of the parasite.



The products and biochemical mechanism of artemisinins' action.
Zongru Guo, Artemisinin anti-malarial drugs in China Acta Pharmaceutica Sinica B, Volume 6, Issue 2, 2016, 115–124.

Artemisia annua possesses the capacity to produce high phenolic compounds, which result in high antioxidant activity. Five major groups (coumarins, flavones, flavonols, phenolic acids and miscellaneous) containing over 50 different phenolic compounds were identified. *Further researches in the **synergistic effect of artemisinin and flavonoids** and their biological interaction between malaria and cancer are needed*.*



Source: Wikipedia

* Ferreira, Jorge F. S.; Luthria, Devanand L.; Sasaki, Tomikazu; Heyerick, Arne (2010-04-29). "Flavonoids from Artemisia annua L. as Antioxidants and Their Potential Synergism with Artemisinin against Malaria and Cancer". Molecules. 15 (5): 3135–3170. doi:10.3390/molecules15053135. PMID 2065746

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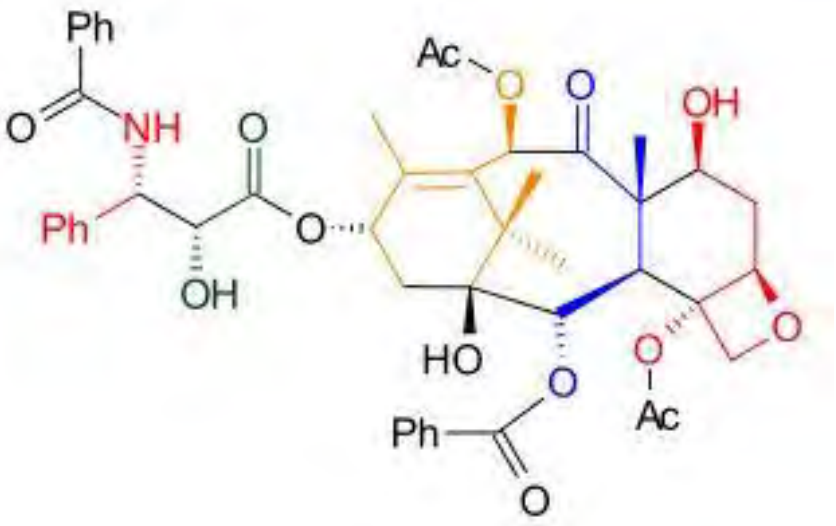
However, why do plants produce phytochemicals/secondary metabolites? Most believe that it is one part of the evolutionary 'battle' between plants and herbivores. Moreover, if one is attacked by clusters of related toxic agents, it is much more difficult to 'escape'; e.g., by a chemical detoxification of the 'poison'. Let us remember, some very strong drugs are derived from plants (e.g., digitalis, colchicin), as are some very toxic poisons (e.g., cicutoxin from Cicuta virosa L.). During the evolution of pharmaceutical chemistry, we searched for THE active principle in plants, isolated the same (if possible), and made chemical modifications to increase its power. Up to now, this is ONE way (and not an inefficient one; e.g., Taxol to discover new medicines. But sometimes the plants are 'the better chemists'.

TAXOL



Source: Wikipedia

The biosynthetic pathway to paclitaxel has been investigated and consists of approximately 20 enzymatic steps. The complete scheme is still unavailable.

The two main reasons why this type of synthesis is not feasible in the laboratory is that nature does a much better job controlling stereochemistry and a much better job activating a hydrocarbon skeleton with oxygen substituents for which cytochrome P450 is responsible in some of the oxygenations.

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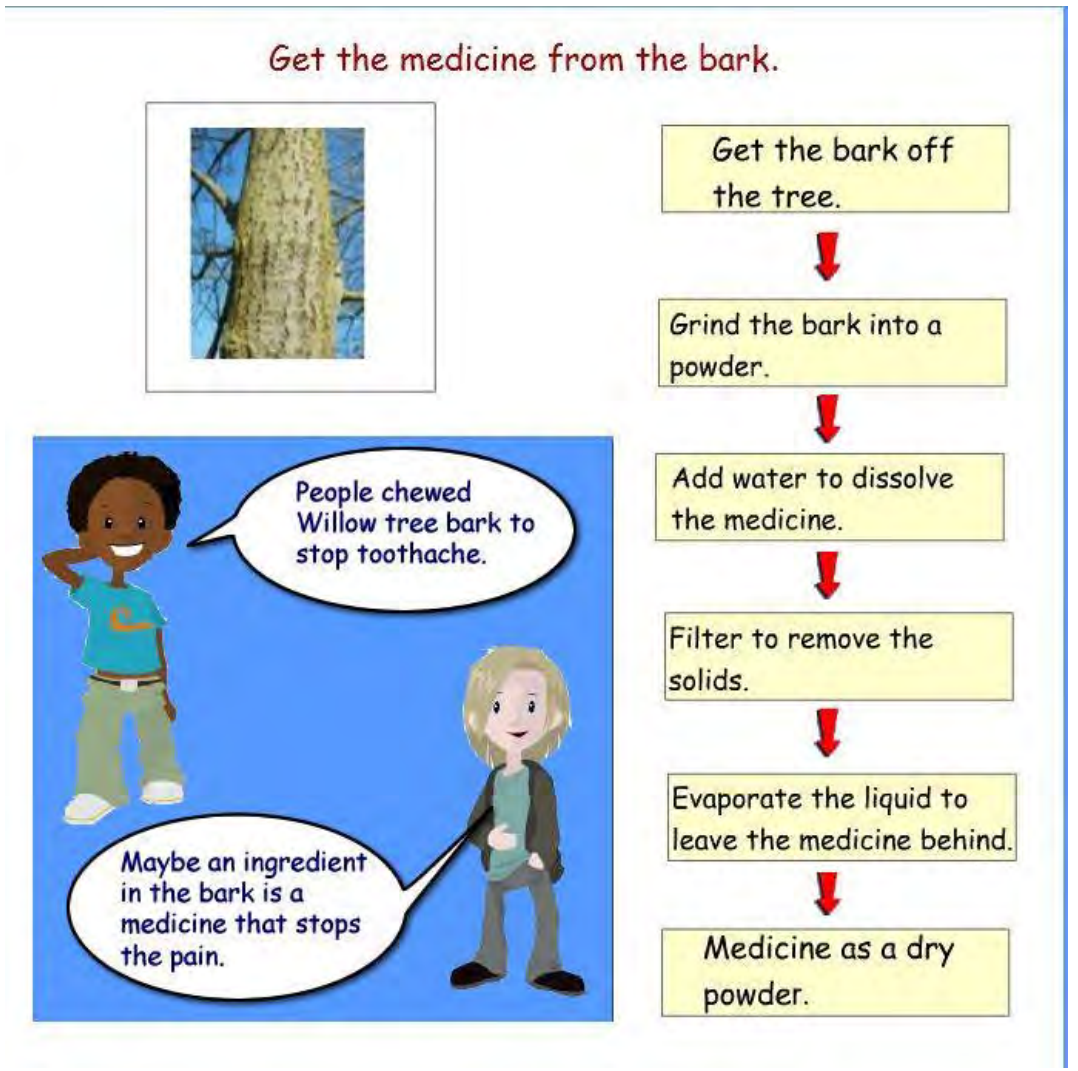
So we can profit from this evolutionary concept of the plants, if we learn our lesson. Our efforts in research should be strengthened to detect several vulnerable sides of "enemies", e.g. cancer-cells or deranged biological pathways or germs and the regulation of the future must follow this concept, if evidence is proven. Nevertheless whether the medicines are chemically defined or from natural origin.

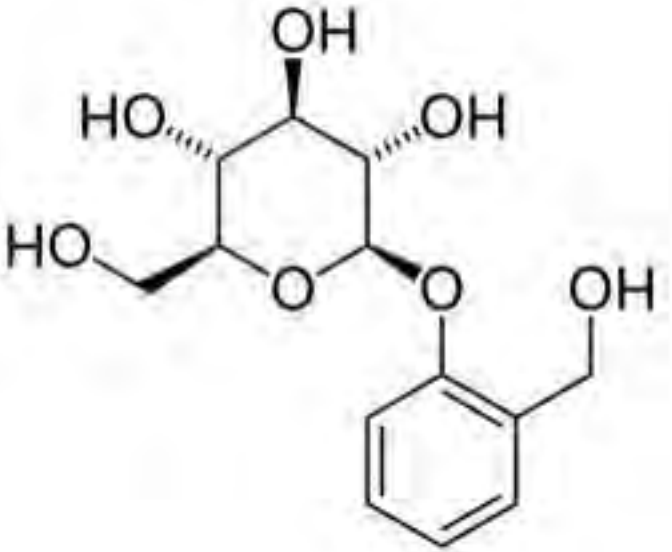
A good example for homo sap. is Willow bark. It has been mentioned in ancient texts as a remedy for aches, fever and pain relief. The Edwin Smith Surgical Papyrus, dating from the seventeenth century B.C.

It is one of the oldest of all known medical papyri.

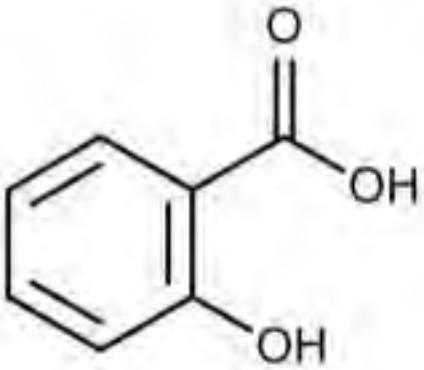


The mode of action of the combination is stronger, as possible compared **to the content of salicin,** therefore synergistic effects of the other containing ingredients are suspected*.

Salicin

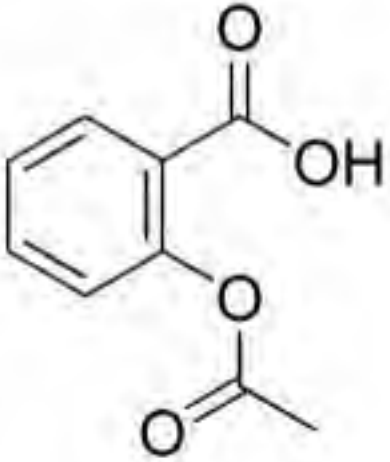


Salicylic acid



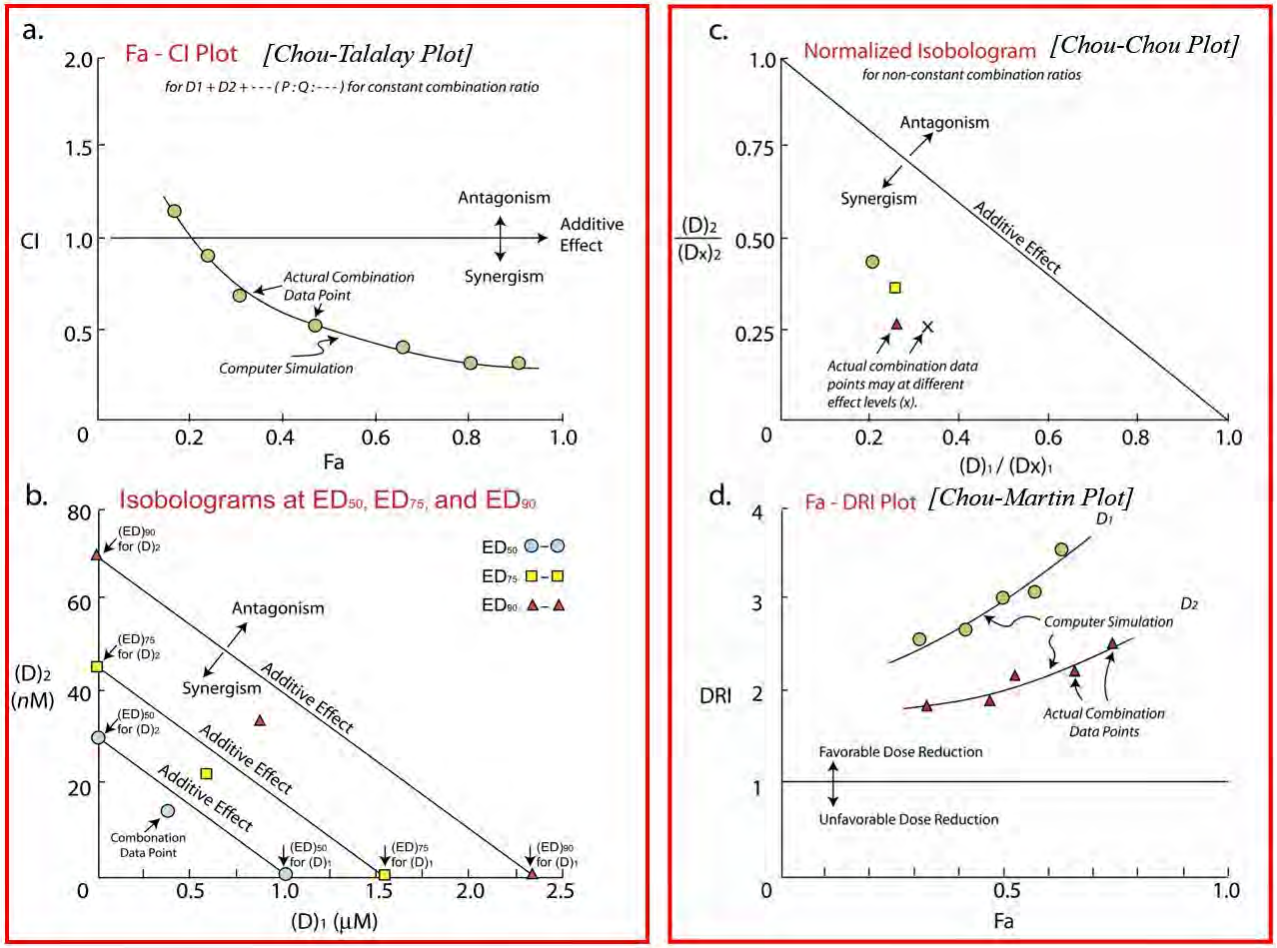
Source: Wikipedia

Acetylsalicylic acid



* E.G: G.A. Bonaterra, E.U. Heinrich, O. Kelber, D. Weiser, J. Metz, R. Kinscherf, Anti-inflammatory effects of the willow bark extract STW 33-I (Proaktiv1) in LPS-activated human monocytes and differentiated macrophages, Phytomedicine 17 (14) (2010) 1106–1113; G. Ulrich-Merzenich, O. Kelber, A. Koptina, A. Freischmidt, J. Heilmann, J. Müller, H. Zeitler, M. Seidel, M. Ludwig, E. Heinrich, H. Winterhoff, Novel neurological and immunological targets for salicylate-based phytopharmaceuticals and for the anti-depressant imipramine, Int. J. Phytother. Phytopharmacol. 19 (10) (2012) 930–939, doi:http://dx.doi.org/ 10.1016/j.phymed.2012.05.004 (Jul 15, Eub 2012 Jun 27).

With respect to my famous colleague Prof. Dr. Ting-Chao Chou I'll show you, that's even possible to make science-based predictions about the effects of SYNERGY:



Therefore, as first conclusion, sometimes you can use „synergy” of combination-treatment to “make the devil an angel”.

Regulatory Consequences

Design of clinical trials for combination use

FDA acknowledges the need for combination therapy in certain conditions and encourages co-development of drugs. They released draft guidance in December 2010 concerning the co-development of novel unmarketed drugs for use in combination and a final guidance for industry on this topic in June 2013. Before the FDA released this guidance, co-development of drugs for a combination regimen was rather challenging as no further assistance in this matter existed. The concept of combination treatment is not new of course but the FDA guidance gives precise requirements and recommendation on how the development should proceed. Regulatory, scientific and medical aspects are addressed. Having a guidance that highlights the importance of drug combinations helps to speed up drug development and reduce costs. It also helps patients gain earlier access to treatment.

The guidance states, that for many serious diseases such as cancer, infections and cardiovascular diseases *"combination therapy is an important treatment modality"*.

Growing understanding of pathophysiological mechanisms helps improving treatment responses using drug combinations. New therapeutic approaches based on this knowledge can be used to our advantage. Due to a higher risk of those combinations compared to single drug use alone combinations should only be developed for serious diseases. Knowledge of the individual active compounds in the combination is lower than that of only one active ingredient developed for the treatment. Therefore, the data concerning the safety profile, effectiveness and dose-response are less informative. The FDA therefore specifies the conditions under which co-development is reasonable.

The combination is intended to treat a serious disease or condition

There is a strong biological rationale for use of the combination (e.g. inhibition of different pathways, lower doses of drug can be administered to decrease toxicity, resistances are reduced)

A full non-clinical characterization of the activity of both, the combination and the individual new investigational drugs, or a short-term clinical study on an established biomarker, suggests that the combination may provide a significant therapeutic advance over available therapy and is superior to the individual agents.

A non-clinical model should demonstrate that the combination has substantial activity and provides greater activity, a more durable response (e.g., delayed resistance), or a better toxicity profile than the individual agents.

There is a compelling reason why the new investigational drugs cannot be developed independently (e.g. risk of resistance, limited activity when used as monotherapy)

Furthermore, the procedure for clinical development is described in the guidance.

The main objective in Phase 1 studies is to determine safety and pharmacokinetics of both the individual drugs and the combination. Whenever feasible, all pharmacokinetic parameters of the individual drugs should be investigated. If it is not possible to characterize the drugs individually in humans, non-clinical studies should be conducted.

Phase 2 should further demonstrate the contribution of each individual new investigational drug in the combination, provide evidence of the combination's effectiveness and adjust the dose(s).

When possible a factorial study design is desirable to obtain as many information about the drugs and their combination.

Three scenarios are conceivable for phase 2 studies:

1. Each new investigational drug alone has activity and they can be administered separately

To obtain the most information about safety and effectiveness the individual drugs alone should be compared to the combination and standard of care (SOC).

2. The individual new investigational drugs in the combination cannot be administered separately

In cases where the individual drug cannot be administered separately for pharmacological or ethical reasons (e.g. ineffectiveness of the individual drug or rapid development of drug resistance) only the combination should be studied.

3. When administered separately, one new investigational drug in the combination is active and one is inactive

The minimally active compound requires Phase 1 safety studies but not a further individual drug Phase 2 study.

The study designs suggested by the FDA for each scenario are given in the Table.

Scenario	Study design	Remarks
1	A v. B v. AB v. SOC or placebo	SOC can be added to each arm, when it is a known effective, not palliative, therapy
2	AB v. SOC	SOC can be added to AB, when it is a known effective, not palliative, therapy, comparing to placebo + SOC
3	A^{*} v. AB^{+} v. SOC or placebo	

Source: FDA

However, *the guidance only concerns novel unmarketed drugs.*

Nevertheless, it can be expected to be found that also drugs that are already marketed can be beneficial in certain combination therapies for specific indications.

Therefore, the FDA guidance takes a step into the right direction but does not go far enough yet.

Therapeutic concepts* **on the other hand would take the next step and would also cover combinations containing compounds that are already marketed to improve the safety of combinations use of these compounds.**

* Kirsten Krollmann und Harald G. Schweim, "Zulassung von „therapeutischen Konzepten“: Der nächste Schritt zu einer „personalisierten“ Medizin ", Pharm Ind. 5, 650 - 654 (2015).
Kirsten Krollmann, „**Therapeutic concepts: Proposing a new regulatory pathway for combination therapies”** PhD thesis, 2017. http://hss.ulb.uni-bonn.de/2017/4676/4676.htm

There exists a gap between treatment reality, including the approval practice, and research. The limits of single drug authorizations have been reached. New pathways for the authorization of combinations need to be introduced. The next logical step in the regulatory framework is the co-approval of combination therapies based on targeted approaches, which so far does not exist. The approach introduced in this paper recommends this additional new way of drug approval to overcome this gap.

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The development and approval of novel therapeutic concepts would be a consistent step towards better health care. A clear regulatory pathway towards an approval of drug combinations could help agencies, health care professionals, and patients to obtain safer therapies and clear recommendations for medical practice. To distinguish between an approved combination regimen and the frequently used term 'combination therapy' that refers to a general therapy consisting of a therapy with multiple medicinal products or other treatment options, a new term is introduced for approved combination therapy:

'Therapeutic concepts using synergy'.

Michael (Mike), Lucifer (Luce), Synergy for the Patient

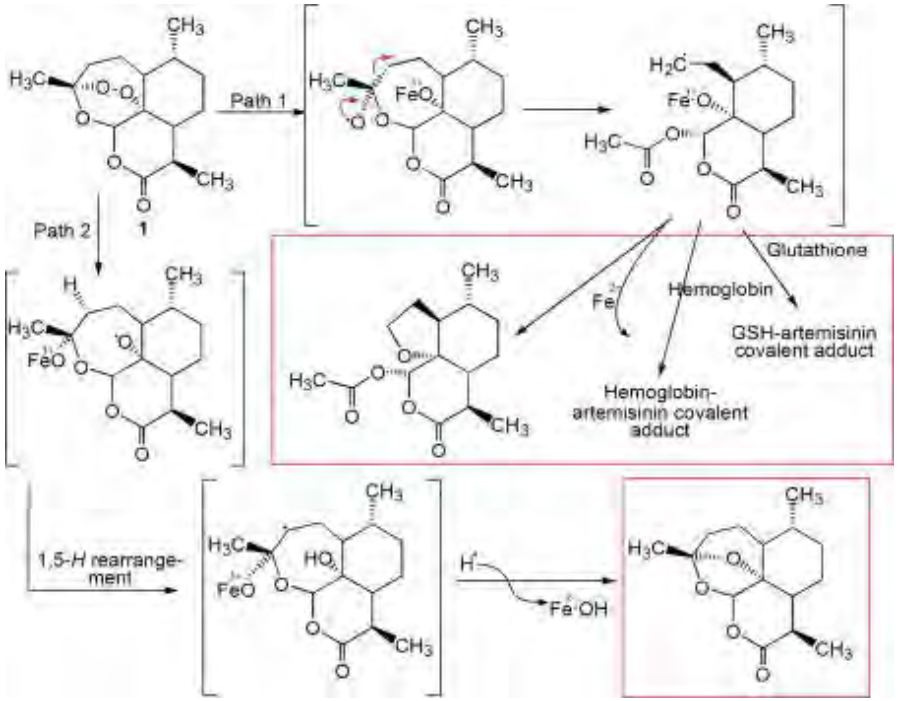
Thanks for Your Kind Attention!

Zongru Guo

Artemisinin anti-malarial drugs in China

Acta Pharmaceutica Sinica B, Volume 6, Issue 2, 2016, 115–124

http://dx.doi.org/10.1016/j.apsb.2016.01.008



Scheme 4. The products and biochemical mechanism of artemisinins' action.

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