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1.Introduction

1. 1 History

Malaria is a clinically manifest and infection [1]. It causes attacks of fever [2]. The malaria pathogen circulates in the red blood cells [2].
The parasites belong to the species *Plasmodium* [1]. *Plasmodium* is the latin term for bad air [1]. This term was extended at the infections with relatives of the family *Plasmodiidae* at the vertebrates [1].
The *Plasmodia* belong to the sporozoa [2]. They are cell parasites [2].

In the article of Wernsdorfer & Wernsdorfer 2010, it was stated that the transmission of the malaria from the humans will be assured through the diptera [1]. The diptera belongs to the species anopheles [1]. They hatch abundantly near surface water [1]. It´s important, that there is in the proximity a food source for the imagos [1]. It is believed that the infections of *plasmodium* exist since the development of mankind in Africa [1]. There are also species specific climatic differences among the *plasmodium* [1]. Thereby are different settlements from *plasmodium* [1]. For example *Plasmodium falciparum* and also *Plasmodium ovale* are in the tropical and subtropical region of Africa [1]. Compared with this exist *Plasmodium vivax* and *Plasmodium malariae* in the moderate latitudes and they could also exist at the edge of the arctic [1].

It is interesting that there are hints of malaria which are found in the Edwin Smith surgically papyrus at 1600 before Christ [3] and also from the Ebers Papyrus at 1550 before Christ [4].
Hippocrates from Kos, approximately 400 before Christ, described as the first author the clinical symptoms of malaria [5]. He described the classical trias which involve fever, shivering and attack of sweating [1]. He also described the periodicity and the danger of the different forms of malaria [1]. Hippocrates from Kos distinguished the tertian malaria from the quartan malaria [2].

Celsus proposed in the 1st century A.D. a classification for the manifestation of the Malaria tropica, quartana and tertian [1]. The positive effects of the cortex of Cinchona sp. in the treatment of malaria were found in the 17th century [1]. Interesting is the history of the use of Cinchona cortex [1]. There was a countess, called Chinchón [1]. She was the wife from the viceroy from Peru [1]. She got this cortex for the treatment of febrile diseases [1].

In the year 1640 this cortex was brought to Europe [1]. It was used for the treatment of malaria diseases [1].

This tree got the name Cinchona from Linné [1]. He called the tree after the countess Cinchón [1]. Afterwards this cortex was called China-bark [1].

In the year 1820 Pelletier & Caventon undertook the extraction of the pure alcaloids [6].

There are four important alkaloids in this cortex [1]. The first one is Chinin with approximately 90 %, the second one is Chinidin with approximately 8 %, the third one is Cinchonin with 1 % and the last one is Cinchonidin with also 1 % [1]. Chinidin is an alkaloid with the highest clinical pathological effect against malaria [1].

A recommended dose was developed for the treatment of the different forms of malaria [1]. In the year 1890 Koch introduced the use of Chinin in hyperendemic regions of East Africa [1].

A big problem was the First World War [1]. It took a big part at the interruption of the supplies of chinin [1]. For example the Danube Monarchy, Germany and also the Turkey were split from the Chinin sources [1]. But also the opposition showed defects [1]. After the war there were synthetic malaria remedies developed [1]. In 1925 Pamaquin was a success [7]. It is an 8-Aminocholin and it is just a weak medicine [7]. But in 1930 another drug was found for the Chemoprophylaxis and also for the treatment of malaria [8]. The name of the drug is Mepacrin or Atebrine [8].

It was used until after the Second World War [1]. Chinin was less well-tolerated then Mepacrin [1].

It came through the Second World War to an intense research in the medicinal therapy and also in the combating of the vectors [1].

In 1945 they were convinced in the malaria of primates that there must have been also an exoerythrocytic stage [9]. There were two researchers which found out, that there is at first a phase of division in the liver that the parasites could develop before invading the blood [10]. The names from the researcher were Henry Short and Cyril Garnham [10].
Another important part in the second world war was 4-Aminochinoline (Chloroquin and Amodiaquin), and the 8-Aminochinolins Primaquin [1].
Another point is that there were residual insecticids from the class of the chlorinated hydrocarbons developed [1]. Another problem is that resistance was also found against insecticides [1].

Another important part in the history took Golgi. In 1885 he discovered two parasites species [11]. He found them in the blood from peoples, which are infected with Tertiana and Quartana [11]. Afterwards they were known under the name *Plasmodium vivax* and *Plasmodium malariae* [12].
In 1922 *Plasmodium ovale* was found [13].
In the 1920´s and 1930´s there were in many reports from new species reported. For example about *Plasmodium knowlesi* [4, 14, 9].
This parasite was found in a macaque [15]. *Plasmodium knowlesi* has a lethal effect for rhesus monkeys [15].
There is an evidence that the *Plasmodium knowlesi* parasite is a zoonotic parasite [16, 9].

Another interesting way took the indanthrene processes [1].
In the year 1890 Romanowsky developed an indanthrene processes with eosin and azure-methylene blue. This process made a differentiation of the blood cells possible. Another point is that you could perceive morphological specifics [17, 18].
Afterwards other modifications were developed for example by Giemsa, Leishman, Field & Wright [1].

The path of infection took also an important part [1]. For example, in 1897 Ross observed the development from *Plasmodium falciparum* gametocytes in Culex, Aedes and also in Anopheles [1].

1. 2 Distribution

The risk of malaria was in the middle of the 19st century for approximately 90% [1]. The regions which were affected were parts of Europe and also of Siberia has been the arctic cycle affected [1]. Other regions were southern parts of Afrika, Southeast of Asia, Canada, Melanesia and also parts of South America [1].
The agriculture took also a big part in the control against malaria [1]. It came to a disappearance of malaria in many regions [1]. Some examples to this are England, Sweden, and parts of Denmark [1].
The WHO referred that this disease is now endemic in 106 countries [19]. There were 225 million cases and 781,000 deaths worldwide per year [19].

Mendis et al. wrote in an article of 2001 about malaria cases of *P. vivax*. For example there are over 50 % which are in the regions out of Africa. Approximately 65% of the these cases are in Southern Asia and also in the area of the Western Pacific [20, 24].
It was stated that *Plasmodium vivax* appears in temperate zones and also in many tropical zones [55, 21]. *Plasmodium vivax* is very scarce in the region of the Western and Central Africa and of the region of sub-Saharan [22, 24].
The problem of this is that the merozoites of *Plasmodium vivax* just invade the erythrocytes of people which are Duffy-positive. But the Duffy-positive individuals occur very seldom in the regions of Africa [23, 24].
47 % of the malaria cases were in Thailand from the parasite *Plasmodium vivax* [25].

Sweden, England and also parts of Denmark are free of malaria [1]. The reason is that from the 19 century, there were many modifications in the agriculture [1]. The malaria was displaced also in the part of North America and also of Europe [1]. The reason about this was that the application of the mechanical methods about the vector control was high [1].
In the years 1945 and 1980 the malaria eradication was in some regions very high [1]. For example in Australia, Europe, USA and also big parts of North America and of Asia [1]. Nowadays the risk of malaria is 40% [1].

The malaria cases which are clinically manifest account annualy for approximately among 300 and 500 million [21]. In contrast to the clinically manifest malaria cases, the deaths have been lying per year among 1,1-2,7 million [21].
I should also like to add that these examples of malaria cases are mainly infections of *Plasmodium falciparum* [1].
In summary, it can be said that, the malaria cases in Africa belong to the highest, with a percentage of approximately 90 % [1]. The next countries are Asia and western area with roughly 10 % [1]. The malaria cases of the regions of America which are lying in the south of US are approximately 1% [1]. These clinically manifest malaria cases are mainly, with a percentage of 90 %, from the parasite *Plasmodium falciparum* [1]. The other one are from the parasite *Plasmodium vivax* [1]. It is important to say, that monoinfections of *Plasmodium malariae* and *Plasmodium ovale* are very rare [1].

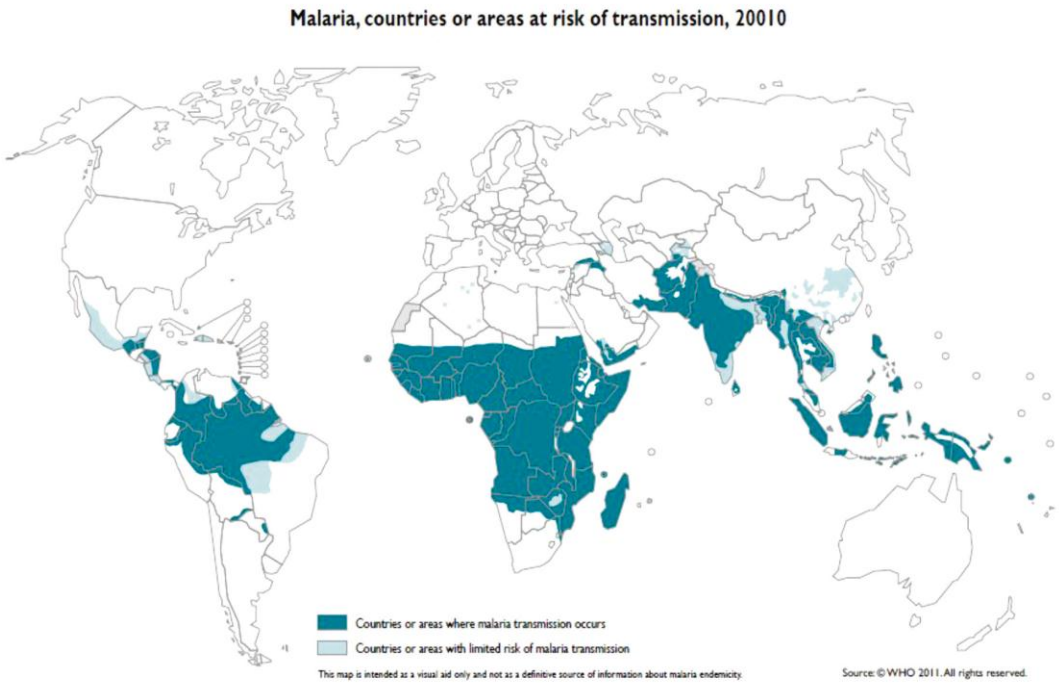

Fig. 1.2.1: Areas of the malaria transmission (WHO 2011)

Source: http://www.fam.at/pdf/rel/FAM-Info_MalariaUpdate2011.pdf

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1. 3 The parasite and the clinical picture

As mentioned at the beginning the malaria parasites belong to the subkingdom of Protozoa [1]. The phylum is called the *Apicomplexa* [1]. They belong to the class of the *Sporozoasida* [1]. The subclass where they belong are called *Coccidiasina* [1]. The order are the *Eucoccidiorida* [1]. The family are the *Plasmodiidae* and the genus was called *Plasmodium* [1]. The genus *Plasmodium* comprises to Garnham 10 subspecies [26, 1].

On that point belong *P. (P.)* with 20 primates-specific species. *P. (Laveriana)* with 2 primates-specific species. *P. (Vinckeia)* with 19 for lemurs and lower mammals specific species, *P. (Haemamoeba)*, *P. (Giovannolaia)*, *P. (Novyella)* and *P. (Huffia)* with 31 for birds specific species [26, 1]. Other ones which take part on this are, *P. (Sauramoeba)*, *P. (Carinamoeba)* and *P. (Ophidiella)* with 40 for reptiles specific species [26, 1].

To the subgenus *P. (P.)* and *P. (Laverania)* belong to 6 important species [1]. The species *P. (L.) falciparum* belong to the subgenus *P. (Laverania)* [27, 1]. This species is just a human pathogen [27, 1]. It is the phylogenetical youngest malaria parasite [27, 1].

To the subgenus *P. (P.)* belong the 2 species *P. (P.) vivax* and *P. (P.) ovale*, which are a human pathogen [1]. *P. (P.) malariae* occurs in humans and also in primates [1]. *P. (P.) cynomolgy* and *P. (P.) knowlesi* belong to the monkeys and rarely in the humans [1].

It´s interesting that the *Plasmodium knowlesi* parasite only causes primate malaria [4]. In association with this, there are quotidian fever pattern [28]. In contrast to the *Plasmodium knowlesi* the merogony cycle of the parasite *Plasmodium malariae* continues 72 hours. The fever patterns at a *Plasmodium malariae* infection do not to be four days [29, 28].

In the southeast of Asia there is a *Plasmodium* species, which is called *P. ovale* [1]. The role of this species is not yet resolved but we know that *P. ovale* shows a high stenoxenie for human beings [1]. Partially it was observed in humans [1]. The life treatening at the *Plasmodium vivax* malaria was very rarely, but this belief has now changed [30, 24]. The malaria tertiana is caused by the parasite *Plasmodium vivax* [24]. In relation to other forms of malaria, malaria tertiana is a harmless form of malaria [24]. The merozoites of *Plasmodium vivax* only infect the reticulocytes [24].

There are different symptoms which characterize the tertian malaria [24]: So the symptoms from the parties concerned are:

a) recurrent fever, which is high [24]
b) shivering [24]
c) anemia [24]
d) arthralgia [24]

One ather point in comparision with this, it is important to say, that the people could get also:

a) cerebral malaria [31, 32, 33, 24].
b) liver dysfunction [31, 32, 33, 24].
c) severe anaemia [31, 32, 33, 24].
d) a respiratory distress syndrome, which is acute [31, 32, 33, 24].
e) a renal failure [31, 32, 33, 24]

Plasmodium vivax and also *Plasmodium ovale* could develop hypnozoites [2]. The problem is, that it could be leading to a relapse they are leading to relapses of the malaria[1]. Just the reticulocytes at *Plasmodium vivax* could be infected [34]. The densities of the limiting of the parasitaemia amounts under 100000/µl blood [34]. The hypnozoites have a span of survival, which could be five years [35, 34].

In relation to other *Plasmodium* species, which are pathogens for human beings, we could say that the incubation interval of *Plasmodium vivax* parasite is one of the shortest [36, 34]. In contrast to the *Plasmodium vivax* parasite, the *Plasmodium falciparum* parasite needs the erythrocyts for the survival [34].

In contrast to the *Plasmodium vivax* infections, the *Plasmodium falciparum* infections have at first in the liver the pre-erythrocytic development and subsequently they are in the blood [37, 34].

There is a special definition for the malaria relapse, which I have seen in a article from Coatney in the year 1976. It predicates that: “re-appearance of parasitemia in a sporozoite-induced infection following adequate blood schizonticidal therapy” [38].

Tab. 1.3.1: The most malaria pathogens for the humans and their characteristics.

Parameter	***P. falciparum***	***P. vivax***	***P. ovale***	***P. malariae***
The afflicted erythrocytes	All stages in the life	reticulocytes	reticulocytes	older red blood cells
The infected erythrocytes	not enlarged	enlarged	enlarged	not enlarged
The multiple infested of the same erythrocytes	often	rarely (but it is often at Plasmodium vivax multinucleatum)	rarely	rarely
The chromatin of the trophozoites	often double	rarely double	simple	Simple
The Pigment	brown/black	yellow/brown, fine	black, rugged	black, rugged
The number of the merozoites in the mature schizont	24-36	16-24	8-12	6-8

The Gametocytes	banana-shaped	round	round	round
The time of the gametocytogony	12 days	48-96 h	48-96 h	72-120 h
The time of the erythrocytic schizogony	48 h	48 h	48 h	72 h
The number of the merozoites in the praerythrozytary schizonts	20000-40000	10000	15000	2000
The diameter of the praerythroytary schizonts	60 µm	45 µm	70 µm	45 µm
The ceiling of the parasitemia	unlimited	150000	150000	rarely >50000
The maximum of the resting time from the infection in the human	4 years	5 years	7 years	life-long

Source: Malaria (Wernsdorfer W. H. & Wernsdorfer G., 2010)

1. 4 The development cycle of *Plasmodium*

The life cycle is, for example for the human malaria of all *Plasmodium* species the same [39]. So there is at first a sexual phase [39]. Such phase is followed by a part which was called sporogony [39]. These was in an anopheline mosquito [39]. Subsequently there is an asexual phase [39]. In this stage there is a erythrocytic and also a preerythrocytic part of schizogony [39].

The female anopheline mosquito injects the malaria sporozoites [39]. After the injection, the sporozoites walk on and leave the bloodstream in just a few minutes [40, 41, 39]. After 48 hours in the liver schizonts could be found [42, 39].

There are three phases which take an important part in the development cycle of Plasmodium. In the book of Wenk & Renz 2003, it was stated about the three phases, which I summarize in the following few pages.

The first one is the phase of invasion:

The sporozoites come through the prick of the insect into bloodstream [2]. It is assumed that they could also come through lymphatic cells [2].

The sporozoites stay in the peripherally blood for approximately 30 minutes [1]. At this time you could detect them [1]. They have achieved either the hepatic or they stay unspecific with an inactivation [1]. This point is related with phagocytosis in the blood [1].

The second phase is the hepatocytes-parasitic phase:

On the first point, the sporocoits left the sinusoid capillary in the hepatic area [2]. They drift to the hepatocytic tissue [2]. They achieve the hepatocytic transgression across the Dissé-room [2]. The last host cell, which was infested builds a parasitophore vacuole [2]. This parasitophore vacuole will be formed around the meront [2]. But the sporozoits could drift also around the Kupffer cells to the parenchyma cells [2]. At this point the molecular docking mechanisms are important [2]. In the hepatocytes which are infected, there is schizogony [2]. After one week the meronts increase not longer, when *P. vivax* have 10 000 or *P. malariae* and also *P. ovale* have 15 000, or when P. falciparum have 30 000 merocoites [2].

At *P. vivax*, *P. ovale* and *P. Cynomolgi* could be a part of the infected sporocoites, when they have achieved the hepatocytes, to convert to hypnocoites [1].
The hypnocoites make no proliferation [2]. Probably the reason is that they could be actived after a strain-specific diapause [2]. There are three consequences due to the unique limited schizogony:
The first point is, when the merocoites are still in the hepatocytes, they don´t expose [2]. The second point is, that the surface of the hepatocytes is intact [2]. There are parasite-specific surface molecules. Interesting is that there is no inflammation [2]. A further point is that there are no granulomas established [2]. The third point is, that the incubation ends [2]. This happens when the transfer of the merocoites in the blood synchronizes [2]. It could be that they become in the hepatic-parasitic phase fever [2]. This stage is called prodromal period [2].

The next phase is called, the erythrocytic-parasitic phase [2]. There are many sporocoites which are at first in the liver and then they break now in the blood [2]. Subsequently they board the red blood-cells [2]. The merocoites build a mononuclear stage [2]. This stage is called the trophozoites [2]. It eats the substance from the red-blood-cells [2]. The shape from the trophocoites at *Plasmodium vivax*, Plasmodium ovale and *Plasmodium malariae* looks like an amoeba [2]. The shape of *Plasmodium falciparum* is at the beginning round, it is focal oblate and it has a nuclear which is marginal [2]. There is an orbital-phase [2]. This part circulates approximately 8 hours in the blood [2]. Subsequently this trophozoites take place in the capillaries from the following organs: The hepatic, the splenic, the brain and the placenta [2]. This is the reason, that you often couldn´t find the stages of division of *Plasmodium falciparum* [2]. But at the in vitro culture you could see all stages of the schizogony [2]. The meronts at the other Plasmodium of the humans stay in the circulated blood [2].
The first four stages of division are nearly free of symptoms [2]. One other important point is, that the parasitemia continues to rise [2]. So the density of the trophozoites increases in the blood [2]. When you sudden get at a Plasmodium falciparum infection with high fever, the letal flooding of the blood is confined [2]. The reason of this is, that the young trophozoites die, when the

body temperature is over 40°C [2]. When the latency of the humoral immune response is at the end, then there is a regulation of the density [2]. Whereby, this humoral immune response is from 6-8 days [2].

When an infected human overcomes at the critical time, begins the maintenance of the parasitosis [2].

At the schizogony and the gamogony the trophozoites metabolize the haemoglobin [2]. This is important for Plasmodium, because it gets amino acids from the protein proportion [2]. It could make this with different proteases by hydrolyzing [2]. The haem is a complex of Porphyrin and Fe^{2+} [2]. It oxidized to ferriprotoporphyrin IX [2]. Subsequently it will be detoxified to a dimer indissoluble hemozoin. The hemozoin is a pigment of malaria [2].

The Plasmodium is also able to glycolyse to get energy [2]. The meronts which were burst released in the chronical phase of the malaria the antigens [2]. The antigens neutralize the antibodies [2]. So the antigens help the merozoites that they can come in the red blood cells before there is a humoral immune response [2].

All in all it is also important to say that a part of these parasites makes a preerythrocytic schizogony which continues for approximately 5 - 15 days [39]. This depends on the different species [39]. The mature schizonts are able to enlarge [39]. The mature schizonts busts and then the merozoites can come in the red blood cells [39]. Subsequently they initiate a schizogonic cycle [39]. The clinical manifestations are associated with this [39].

On the first stage of the infection the parasites will develop gametocytes in the humans [2].

When they come into the anopheles mosquito, they develop in the stomach microgametes and macrogametes [2].

In the ookinetes was done a development of the zygotes [39]. Then they drift through the stomach wall [39]. Then they form the oocysts [39]. This was done out of midgut [39]. Subsequently when the oocysts which are ready, bursts and then they liberates about thousands of the sporozoites [39]. They walk from the salivary glands and then they migrate to other human host cells who gets pricked by the mosquito [39]

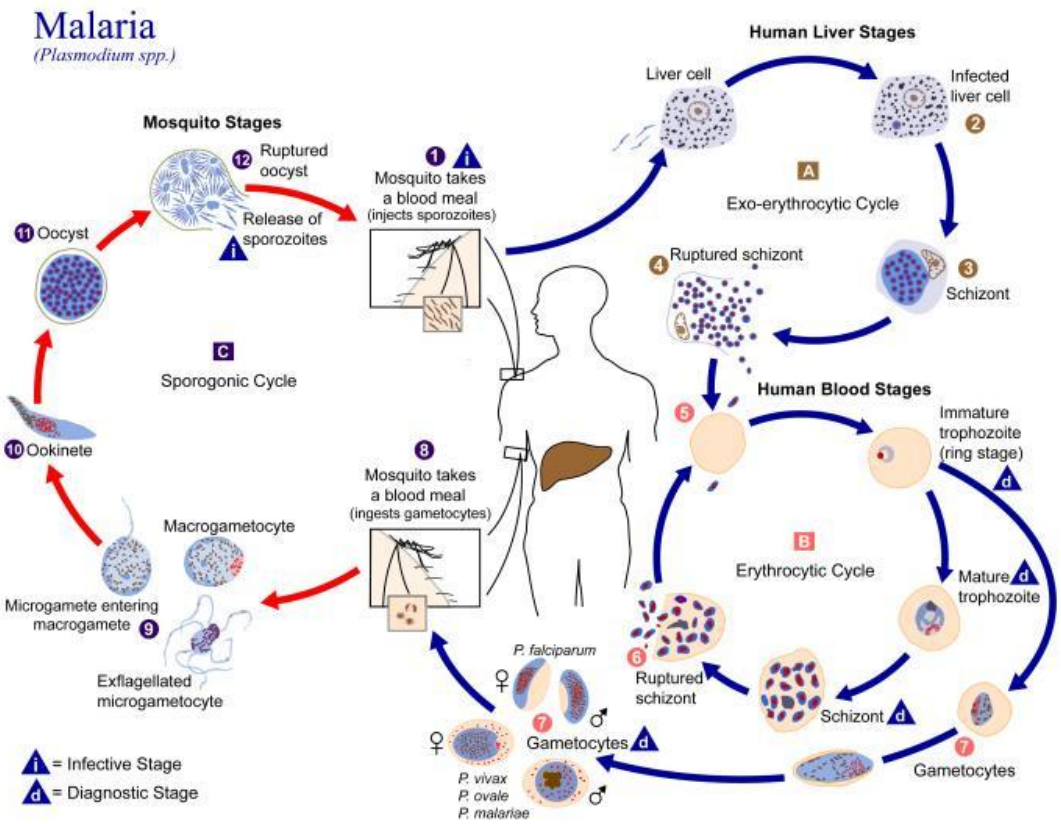

Fig. 1.4.1: The life cycle of Plasmodium

Source: http://hardinmd.lib.uiowa.edu/pictures22/cdc/PHIL_3405_lores.jpg

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1. 5 The vector

In the article of Wernsdorfer & Wernsdorfer about Malaria, from the year 2010, they stated also about the vector.

The subgenus of *Plasmodum* – *Laverania* and of *Plasmodium* – *Plasmodium* are among to the diptera from the genus of anopheles [1]. It is necessary to say, that just the female mosquitos can transmit the malaria parasite [1]. The reason is that only the female mosquitos take blood [1]. There are approximately 420 species of Anopheles mosquitos [1]. But only 29 of them can transmit malaria [1].

Interesting is also the way of life of them. The Anopheles mosquitos are nocturnal [1]. They take the bloodmeal in the time between the dusk and dawn [1]. Also the egg deposit ensued in the same time [1]. The development of the vector is the following:

At first the development is dependent of the temperature [1]. For example in regions of the tropical lowland is the development just one week [1]. The larvaes hatch between 24-36 hours [1]. That is the first phase of the larvae [1]. To the fourth phase of the larvaes vanish approximately 4-5 days [1]. Afterwards the nymph is ready [1]. The evolved imago is ready in 24-48 hours [1]. Subsequently the imago breaks out from the nymph [1].

The development takes a longer time in other regions where the climate is cooler [1].

Tab. 1.5.1: The 29 species of Anopheles which are singnificant vectors of malaria.

	Species	**Incidence**
Robust malaria	A. Arabiensis *PATTON, 1905*	Tropical Africa, South West - Arabia
	A. fluviatilis *JAMES, 1902*	South East Asia
	A. funestus *GILES, 1900*	Tropical Africa
	A. gambiae ss *GILES, 1902*	Tropical Africa
	A. melas *THEOBALD, 1903*	Tropical Africa
	A. minimus minimus *THEOBALD, 1901*	South East Asia
	A. sacharovi *FAVRE, 1903*	Europe, West-Asia
Intermediate stability	A. atroparvus *VAN THIEL, 1927*	Mediterranean region
	A. dirus *BAISAS, 1936*	South East Asia
	A. quadrimaculatus SAY, 1824	US
	A. sergenti *THEOBALD, 1907*	South West Asia
	A. sundaicus *RODENWALDT, 1925*	Littoral South East Asia
Instable malaria	A. aconitus *DÖNITZ, 1902*	South East Asia
	A. albimanus *WIEDEMANN, 1820*	Central- and South America

	A. annularis *VAN DER WULP, 1884*	South East Asia
	A. aquasalis *CURRY, 1932*	Central- and South America
	A. culicifacies *GILES, 1901*	South Asia
	A. darlingi *ROOT, 1926*	South America
	A. farauti *LAVERAN, 1902*	The area of the western pacific
	A. hyrcanus sinensis *WIEDEMANN, 1828*	South East Asia
	A. labranchiae *FALLERONI, 1926*	Europe and West Asia
	A. maculatus *THEOBALD, 1901*	South East Asia
	A. messeae *FALLERONI, 1926*	Europe and West Asia
	A. minimus flavirostris *LUDLOW, 1914*	South East Asia
	A. pharoensis *THEOBALD, 1901*	North East Africa and Sahelian zone
	A. philippinensis *LUDLOW, 1902*	South East Asia
	A. punctulatus *DÖNITZ, 1902*	New Guinea
	A. stephensi *LISTON, 1901*	South Asia western of Myanmar
	A. superpictus *GRASSI, 1899*	Europe, West Asia

Source: Malaria (Wernsdorfer W. H. & Wernsdorfer G., 2010)

1. 6 The vector control and treatment

The prevention is an important point in this unit [19].

Such points were from the WHO 2010 stated, which I summarize.
There are important aims of control of the vectors:
For this point it is important to reduce their longevity [19]. Another point is to control the vector density [19].

There are two interventions which are important for the vector control [19]. On the one hand it should give a long-lasting insecticide-treated mosquito net and on the other hand it should give an indoor residual spraying which takes an important part [19].

The treatment with antimalarials is not only important. The exposure prophylaxis also takes an essential part. For example you should use repellents like icaridine and diethyltoluamide.

1. 7 Treatment with antimalarials

One treatment is the primaquine therapy [24]. At this treatment there are also problems [24]. It is not good for humans which contraindicated in patients which have a glucose-6-phosphate dehydrogenase deficiency [24]. It is also a problem for humans which are younger than four years [24]. The last point is, that it is also not good for women which are pregnant [24].

In the WHO 2001 it was stated that the standard therapy for people which are infectet with *Plasmodium vivax* is Chloroquine [43].

The highest risk of resistance was eastern part of the Indonesia and also Papua [44].

Other regions were Indonesia, Myanmar [45], and also South-East Asian regions [44].

But it is also important to mention that there were found also resistances of Plasmodium falciparum against chloroquin [1]. The resistances occurred in the border regions of Thailand and Cambodia and also in Venezuela and Colombia [46, 47].

There were also found other resistences against chloroquine were in the region of Southeast Asia, of South Amerika and Africa [1]. Nowadays, *Plasmodium falciparum* shows just in Central America resistance against chloroquine [1].

Chloroquine had just an effect against the different blood stages [2].

Pyronaridine is an alternative to chloroquine [24]. There is a study which shows a synergism of the antimalarial pyronaridine and the antimalarial retinol [24]. The study was done in *Plasmodium vivax* [24].

In another interesting study there was found also a synergism in other antimalarials [34]. The drugs which were tested are mefloquin, chloroquine, and artemisinin of *Plasmodium vivax* [34]. The study was done in northwestern Thailand [34]. The results had shown that there was no significant difference at all the three drugs [34].

The resistance pressure to antimalarials ascends [48]. As compaired with this, *Plasmodium* also makes single and a multiple-mutations [48]. It is important to say that they could make also point-mutations [48].

A combination therapy with the drug artemisinin with other antimalarial-drugs is very helpful [49].

In summary, it can be stated that the antimalarial chloroquine will be gladly taken in areas where it is effective [19]. But it is a problem in regions where *Plasmodium vivax* shows resistances against chloroquine [19]. The WHO 2010 shows the regions which shows resistances. For example as Indonesia, at Myanmar, at Thailand, at Malaysia, at Brazil, at Solomon Islands, at Ethiopia, at Peru and the last one was at Papua New Guinea [19]. In such regions it could use an combination therapy with the drug artemisinin [19].

In contrast to the treatment of *Plasmodium vivax*, the treatment of *Plasmodium falciparum* is:
In Central America the chloroquine therapy is effective [19]. Also the combination therapy with the drug artemisinin could be taken for a Plasmodium falciparum infection [19]. It is essential to say, that the antimalarial artemisinin and also his derviates should not be taken orally [19]. One reason to this is that an oral monotherapie of these derivates could lead to resistances [19].
Approximately 21 African countries use artesunate-amodiaquine [19]. A study has shown, that this countries were 6 with more than 10% of a treatment failure. So the treatment failure shows also a big problem in many countries [19].
As time passed, the pressure of resistance to the antimalarials shows a big problem [19].

2. Material and methods

2. 1 Drugs:

2. 1. 1 Artemisinin

The plant Artemisia annua L. has been known for a very long time [50, 52]. For approximately more than 2000 years this plant took an important part in the traditional medicine in China [50, 52]. Artemisinin was at first in the 1970s isolated [50, 25].

As previously mentioned, this plant has been appropriated from the traditional medicine [51]. There was a team which investigated approximately for example 2000 recipes [51]. They all were traditional herbs [51]. Interesting is that they found out, that there are 640 recipies which show an antimalarial activity [51]. They tested many recipies of these in a rodent malaria and they found out, that the extracts from this plant inhibit the parasite growth [51]. One important person of this team was Youyou Tu [51]. He make a neutral extract [51]. These one had a toxicity which was low [51]. Interesting is, that the antimalarial activity was improved [51].

This drug has saved the live from many humans. Since the late 1990s it was at the very front of the treatment against malaria [51].

The chemical structure of artemisinin is have the following elements: It is a sesquiterpene lactone [52]. These one have a peroxy group [52]. It is a good drug which will be introduced against malaria [52]. This drug has a low toxicity [52].

The antimalarial activity caused by the endoperoxide group [51].

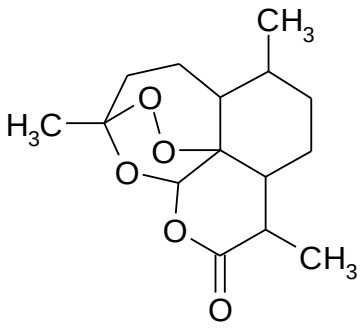


Abb. 2. 1. 1. 1: Structural formulae of artemisinin

Source: Preparation of molecularly imprinted polymers for artemisinin based on the surface of silica gel (Gong & Cao, 2011)

2. 1. 2 Eurycoma longifolia

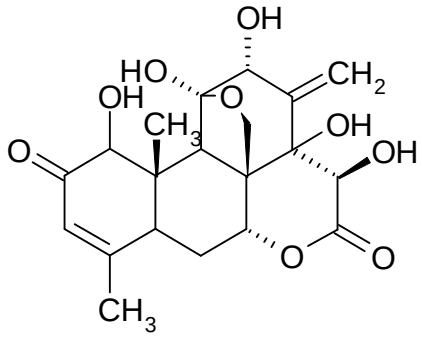
Eurycoma longifolia Jack is the name of the tree [53]. It is an evergreen tree which is flowering and also slim [53].

The tree exists in the jungle of Malaysia and also in Indonesia [53]. This tree could growth to 15 meters [53]. There is a variation of tree products, which found also an application in the folk medicine [53]. It was called Tongkat Ali and Pasak Bumi [53]. It could be used as antimalarial [53]. It has also anabolic properties and also antipyretic properties [53]

There are also early studies [54] which reported that there´s a bioactivity-guided fraction [53]. Eurycoma longifolia has a activity which was potent antiplasmodial than chloroquine [53].

When the purifaction of this fraction is ready, there are three quassinoid constituents [53]. They are called, eurycomanone, 13α(21)-epoxyeurycomanone and 13,21-dihydroeurycomanone [53].

There is a study of eurycoma longifolia [53]. It was tested at *Plasmodium falciparum* [53]. The results from this study are, that there´s a synergism between the quassinoids [53].



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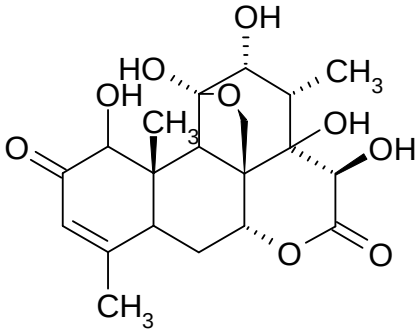

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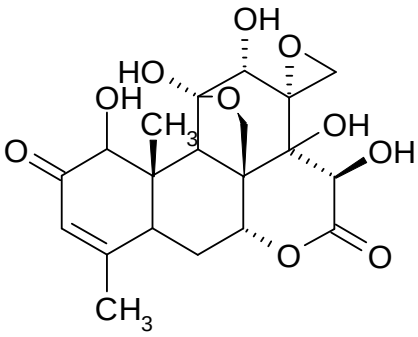

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Abb. 2.1.2.1: Structural formulae of the major quassinoids in the standardizided

Eurycoma longifolia extract:

1 = eurycomanone

2 = 13,21 –dihydroeurycomanone

3 = 13α(21)-epoxyeurycomanone

Source: Activitiy of Eurycoma longifolia root extract against Plasmodium falciparum in Vitro (Wernsdorfer et al., 2009)

2. 2 Testing

For a testing from *Plasmodium vivax* it is better to make an in vitro test [55]. It is better, because you could have a look at the sensitivity [55]. This is an essential difference to the in vivo test [55].

The young trophozoites could mature to the stage of the schizonts of two *Plasmodium* parasites which are called *Plasmodium falciparum* and *Plasmodium vivax* [55]. They could mature to the schizont stage [55]. But they must be incubated at a temperature of 37°C [55]. This is being done in a defibrinated blood supported [55]. These one is with glucose [55].

Subsequently a micro technique will be used. It is for testing of the sensitivity of a drug. For this point it will be taken a RPMI-1640 medium. Such medium could favoured the growth [56, 55].

It is important to say, that in *Plasmodium vivax* are different asexual forms of this parasite, which are very different [55]. So this could be a problem of the evaluation [55]. The reason of this is, that it is requiring a special attention [55].

2. 2. 1 In vitro test:

In the article of Wernsdorfer et al., from the year 2009, it was also stated the in vitro test, after which I would like to refer to.
So for this test there are a few points important:
You should take 200 µl blood [53]. For this point it is important to give it in sterile tube [53]. Such one should be a heparinized and also a capillary tube [53]. They were than diluted with an RPMI-1640 medium [53]. This mixture was taken in an incubator with a temperature of 37,5°C for a time of 3 hours [53].

For the test it should be noted the test series from well A-H [53]. In well A is no drug. It is for the control [53]. From B-H there was the extract of the antimalarial [53]. The concentration ascends from B-H [53].

When the incubation is ready, it is important that they closed the plates [53]. Then they were given in a container with a candle [53]. Subsequently they were given in an incubator [53]. They were placed in it for a time of 23,5 hours at a temperature of 37,5°C [53]. When the incubation is ready, the tests will be harvested [53]. Thereby the supernatant fluid from the wells will be decanted [53]. And then the thick films were prepared [53]. The result is that there were 8 films on one slide [53]. At the end, it is important to give the films in a Giemsa solution for colouring [53].

2. 2. 2 Evaluation of the tests:

For the evaluation the slides were read with the microscope [53]. It is important that we have a magnification about 1000x [57].

But for the evaluation you should know the eight forms of parasites which are distinguishable [55].

The young trophozoite, the medium-grown trophozoite, the advanced trophozoite, the early pre-schizonts, the late pre-schizonts, the mature schizonts, the early gametozyte and the late gametozyte [55].

In the article of Tasanor et al, was stated about the eight forms of parasites. They started with the young trophozoites [55]. The diameter of the young trophozoite is approximately 4 µm [55]. It is particularly important that the form of the trophozoites [55]. They can look like a chromatin with cytoplasm [55]. The chromatin could It can also linked with a ring of a vacuole [55]. With an essential relevance is also the pigment of the young trophozoites [55]. You can not see the pigment [55].

The next stage is the medium-grown trophozoite [55]. The diameter of the medium-grown trophozoite is approximately 4-8 µm and they have a single bead of nuclear chromatin [55]. In this stage the cytoplasma could be separate [55]. But it can be also linked in a ring with an amoeboid structure [55]. As compared to the young trophozoite, the pigment could be seen, but not always [55].

To the advanced trophozoite, here is the diameter bigger than 8 µm and they have a big chromatin [55]. At this time the cytoplasma looks like an irregular ring and it often has a big vacuole [55]. You could also see the pigment [55].

The early pre-schizonts have a chromatin with dots [55]. You can see to 7 points [55]. The nuclear segments look like good defined [55]. And the characteristics of the form are, that it is deep-stained and also ovoid or they could have also round forms [55]. In the early pre-schizonts the pigment could make an aggregation [55].

To the late pre-schizonts we could say, that they have nuclear segments which are defined [55]. In contrast to the early pre-schizonts, the cytoplasm is on the one hand looser and on the other hand it begins to make a condense [55]. This

process is around the nuclei [55]. One other important point is the aggregation of the pigment [55].

In the mature schizonts, the segmentation of the whole cytoplasm is now ready [55]. The chromatin bodies armed with cytoplasm [55]. In contrast to the other schizonts, the pigment granules are concentrated and they they could look like a single round mass [55]. Important for the mature schizonts is, that the merozoites varies between 12 and approximately 24 [55].

The diameter from the early gametocyte is approximately 5 µm [55]. The chromatin is now in the cytoplasm [55]. In the early gametocyte it is not a vacuole [55].

To the late gametocyte, it has a diameter from approximately 5µm, but it could be also bigger [55]. The chromatin is now a single mass and there is also no vacuole [55]. It is also important to say, that the pigment granules are spread [55].

The first plate is for the pre-incubation with a time about 0 hours [55].

There are some criteria which are important for the pre-incubation plate [55]. The first one is, that the pre-schizont count should not be over 10 to 200 parasites which are asexual [55]. Another exclusion criteria is when there are over 5 schizonts which are mature at the 200 parsites which are asexual [55]. The computer program which was taken was Excel.

2.3 Data analysis

Subsequently a data analysis will be done [55]. You have a look at the stage composition prior and after the incubation [55]. It is essential to know that you should count in each film 200 parasites which are asexual [55].

In the analysis the counts from the parasites were multiplied with a specific multiplier [24]. The multiplier for the young trophozoits was 0,75 [24]. The multiplier for the medium-grown was 2,75 [24]. The same multiplier is taken for the advanced trophozoites [24]. The multiplier for the pre-schizonts was 4,5 and at last the multiplier for the advanced schizonts was 5,5 [24]. Subsequently you should add the results and so you get the individual Population Indicator [24].

There are three points which are important criteria for a valid test. The first one is, that the pre-incubation population indicator should be of approximately <400 [24]. As compared to the pre-incubation plate, the post-incubation population indicator in well A should be 100 points bigger [24]. And the last one is that it should be a reduction of the following population indicators [24].

2.4 Log-probit analysis

The results were analyzed with the log-probit method of Litchfield and Wilcoxon [58].
This is important, because you could make afterwards an exact log probit regression which shows also the dose effect.
The analysis where taken now and has been adopted for the computer [59].
Important results for the dose effect were for example the results of EC50, EC90 and EC99 which I will show at the results [55].

2.5 Study region and patients

The study region was in Mae Sot. There is a clinic where all the blood samples for this study were taken.
The region Mae Sot lies at the border of the state of the province which was called Tak [24]. These region is near Myanmar [24].
The studies were done in the year 2010.

For the studies were taken 47 patients. The origin of the infection country was at 31 of the patients in the region of Myanmar. For the rest of the patients, the origin of the infection country was in the region of Thailand.
The residence country was for 26 of the patients in Myanmar and for all the other one in Thailand.
There were 32 males and 15 females. The most of the patients were workers or farmers. There were also some students and forestry workers.
Interesting is the number of days of symptoms, before they have started with the treatment. The most of the patients have started with the treatment after three to four days of fever.

3. Results

In the studies of my diploma thesis there may be used 47 patients. In all the studies the number of isolates, which were taken, was 31, i. e. all isolates from the border region.

In this study it was interesting to know the pharmacokinetic interaction between the 3 standardized formulations of eurycoma longifolia extracts.

In the end of the studies, we would like to know if there is a synergism between the 3 standardized formulations of eurycoma longifolia extracts in combination with artemisinin.

We used different forms of evaluations. One important point is the log-probit analysis. As mentioned already, this evaluation is essential for the dose effect of the different forms of eurycoma longifolia and of artemisinin.

For the evaluation of the results it is important to know some essential points. One example is the heterogeneity which was $\chi^{2.}$ If the heterogeneity is <1,30 then χ^2 is low. One other point is the correlation coefficient which is r. If it is >0,97 then r is relatively high. The next one is the slope function. This variable shows, if the regression is slow or fast. The conversion factor from the slope function is fs [58].

At the end we have a look at the synergism. So we have done a variance analysis.

There is a book from Swaroop et al. It is from the year 1966 and they stated about the statistical methods. The term which was important at this is the probability that the difference is merely due to chance [60].

$$t = \frac{x1-x2}{\sqrt{(v1+v2)* {}^{1}/_{\eta}}}$$

x1 and x2 denoting the difference of the incidences, 2n the double of cases incorporated in the analysis, and v1 as well as v2 the variances between the two sets of figures [60].

3. 1 Artemisinin

The valid results have shown the following values.

The number of the isolates where it applies was 31. These isolates were suitable for the in vitro test.

Tab. 3.1.1: The drug concentration in nmol/l of Artemisin and the inhibition of the schizonts maturation (SMI) in percent.

Drug conc.	SMI%
3,0	20,17
10,0	43,19
30,0	59,31
100,0	74,92
300,0	86,59
1000,0	94,48
3000,0	97,51

It is clearly recognizable that from the drug concentration of 3 nmol/l to 3000 nmol/l a maturation inhibition of the schizonts from 20,17 % to 97,51 % was observed.

Tab. 3.1.2: The regression parameters[1] for Artemisinin

n =	30	S =	11,7893	f_S =	2,1350
a =	3,8174	A =	2,6361	f_{EC-50} =	1,8661
b =	0,4031	K =	7	f_{EC-90} =	3,2116
r =	0,9971	N' =	120	f_{EC-95} =	4,0484
χ^2 =	0,3481	R =	1000	f_{EC-99} =	6,6087

In the table 3.1.2 are the regressions parameters where you can see if the antimalarial have a slow or a fast effect.

So the regression parameters show the following interesting results. One important point is the slope function which was 11,7893. The value of the correlation of regression was in this study, with an result of 0,9971 relatively high, because it was more than 0,97. Another point is χ^2 where you can see the heterogeneity. In this study it was relatively low, because the result was 0,3481. The factor of the slope function was 2,1350. The factors of EC´s shows the following values: The f_{EC}– 50 was 1,8661, the f_{EC}-90 was 3,2116, the f_{EC}–95 was 4,0484 and the f_{EC}–99 was 6,6087.

[1] From Litchfield & Wilcoxon (1949): n= number of isolate; a= intercept of regression; b= slope of regression; r= correlation of regression; χ^2= heterogeneity; S= slope function; A= intermediate term for fS; K= number of drug concentrations; N´= number of points from EC 16 to EC84; R= factor of the highest compared to the lowest concentration tested; fs= factor of S; f_{EC}= multiplication or division factor for obtainin 95 % confidential intervals of EC

Tab. 3.1.3: The mean EC levels for Artemisinin and the 95 % confidential intervals

EC	Mean	95% Confidence Intervals Lower	Higher
EC_1	0,0586	0,0089	0,3872
EC_{16}	1,5947	0,8545	2,9759
EC_{50}	18,8001	10,0744	35,0834
EC_{84}	221,6402	118,7698	413,6097
EC_{90}	451,8291	140,6855	1451,1054
EC_{95}	1112,7533	274,8624	4504,8723
EC_{99}	6033,2202	912,9270	39871,4745

In the table 3.1.3 you can see the different means of EC which show you the effective doses. The mean of the EC 50 was 18,8001, of the EC 90 was 451,8291 and of the EC 99 was 6033,2202. The unit of the means of EC is nmol/

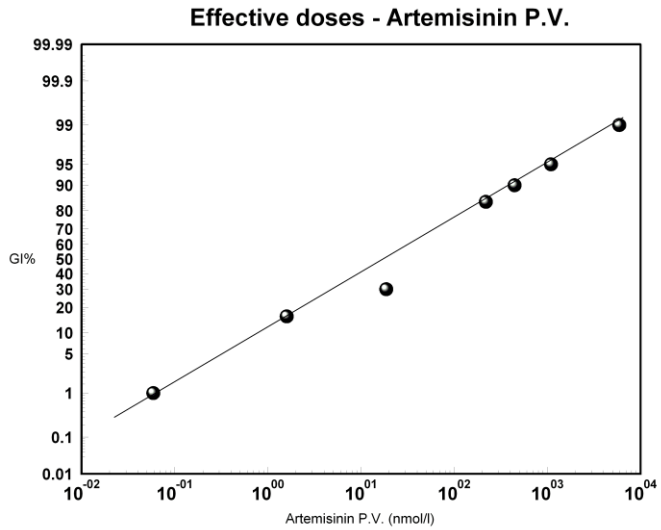

Fig. 3.1.1: The log-probit regression for Artemisinin

From the means of the EC´s in the Fig. 3.1.1 the log-probit regression of the effective doses of Artemisinin are shown.

3. 2 Eurycoma longifolia 1

The valid results have shown the following values.

The number of the isolates where it applies was 31. These isolates were suitable for the in vitro test.

Tab. 3.2.1: The drug concentration in nmol/l of Eurycoma-1 and the inhibition of the schizonts maturation (SMI) in percent.

Drug conc.	SMI%
3,0	28,67
10,0	45,03
30,0	57,72
100,0	69,43
300,0	82,26
1000,0	90,53
3000,0	94,59

It is clearly recognizable that from the drug concentration of 3 nmol/l to 3000 nmol/l a maturation inhibition of the schizonts from 28,67 % to 94,59 % was observed.

Tab. 3.2.2: The regression parameters[2] for Eurycoma-1

n =	31	S =	23,6325	f_S =	2,9939
a =	4,1132	A =	4,9173	f_{EC-50} =	2,0211
b =	0,3145	K =	7	f_{EC-90} =	4,9025
r =	0,9988	N' =	155	f_{EC-95} =	6,9682
χ^2 =	0,1095	R =	1000	f_{EC-99} =	14,4586

In the table 3.2.2 are the regressions parameters where you can see if the antimalarial has a slow or a fast effect.

So the regression parameters show the following interesting results. One important point is the slope function which was 23,6325. The value of the correlation of regression was in this study, with an result of 0,9988 relatively high, because it was more than 0,97. Another point is χ^2 where you can see the heterogeneity. In this study it was relatively low, because the result was 0,1095. The factor of the slope function was 2,9939. The factors of EC´s shows the following values: The f_{EC}– 50 was 2,0211, the f_{EC}-90 was 4,9025, the f_{EC}–95 was 6,9682 and the f_{EC}–99 was 14,4586.

[2] From Litchfield & Wilcoxon (1949): n= number of isolate; a= intercept of regression; b= slope of regression; r= correlation of regression; χ^2= heterogeneity; S= slope function; A= intermediate term for fS; K= number of drug concentrations; N´= number of points from EC 16 to EC84; R= factor of the highest compared to the lowest concentration tested; fs= factor of S; f_{EC}= multiplication or division factor for obtainin 95 % confidential intervals of EC

Tab. 3.2.3: The mean EC levels for Eurycoma-1 with the 95 % confidential intervals

EC	Mean	95% Confidence Intervals Lower	Higher
EC_1	0,0103	0,0007	0,1486
EC_{16}	0,7101	0,3513	1,4352
EC_{50}	16,7812	8,3029	33,9169
EC_{84}	396,5803	196,2170	801,5409
EC_{90}	988,2038	201,5699	4844,7043
EC_{95}	3137,6327	450,2788	21863,6507
EC_{99}	27396,0087	1894,7884	396108,2335

In the table 3.2.3 you can see the different means of EC which show you the effective doses. The mean of the EC 50 was 16,7812, of the EC 90 was 988,2038 and of the EC 99 was 27396,0087. The unit of the means of EC is nmol/l.

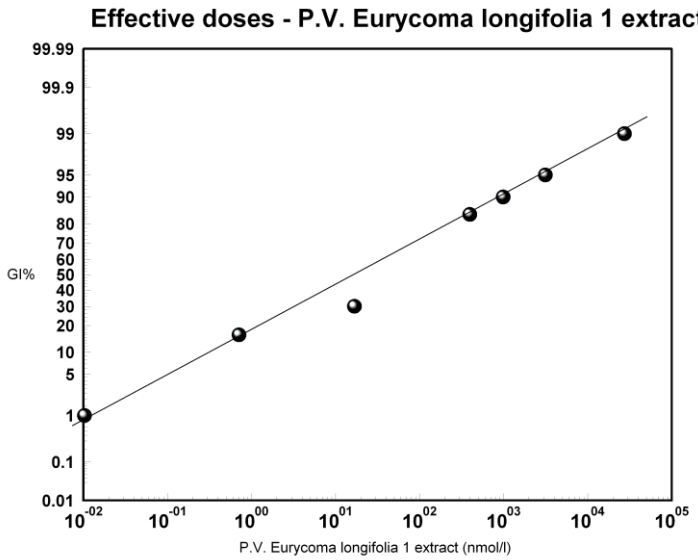

Fig. 3.2.1: The log-probit regressionfor eurycoma-1

From the means of the EC´s it arose in the Fig. 3.2.1 the log-probit regression of the effective doses of the eurycoma longifolia 1 extract.

3. 3 Eurycoma longifolia 2

The valid results have shown the following values.

The number of the isolates where it applies were 31. These isolates were suitable for the in vitro test.

Tab. 3.3.1: The drug concentration in nmol/l of Eurycoma-2 and the inhibition of the schizonts maturation (SMI) in percent.

Drug conc.	SMI%
3,0	30,90
10,0	47,68
30,0	62,14
100,0	72,81
300,0	81,96
1000,0	91,01
3000,0	95,13

At the drug concentration of 3 nmol/l to 3000 nmol/l the maturation inhibition of the schizonts amounts to 30,90 % to 95,13 %.

Tab. 3.3.2: The regression parameters[3] for Eurycoma-2

n =	31	S =	25,8468	f_S =	3,1885
a =	4,2102	A =	5,3884	f_{EC-50} =	2,0618
b =	0,3058	K =	7	f_{EC-90} =	5,3234
r =	0,9983	N' =	155	f_{EC-95} =	7,7333
χ^2 =	0,1474	R =	1000	f_{EC-99} =	16,7669

The table 3.3.2 informs about the regression parameters where the antimalarial have properties are identifiable.

The regression parameters show the following interesting results. One important point is the slope function which was 25,8468. The value of the correlation of regression was in this study with an result of 0,9983 relatively high, because it was more than 0,97. Another point is χ^2 where you can see the heterogeneity. In this study it was relatively low, because the result was 0,1474. The factor of the slope function was 3,1885. The factors of EC´s shows the following values: The f_{EC}– 50 was 2,0618, the f_{EC}-90 was 5,3234, the f_{EC}–95 was 7,7333 and the f_{EC}–99 was 16,7669.

[3] From Litchfield & Wilcoxon (1949): n= number of isolate; a= intercept of regression; b= slope of regression; r= correlation of regression; χ^2= heterogeneity; S= slope function; A= intermediate term for fS; K= number of drug concentrations; N´= number of points from EC 16 to EC84; R= factor of the highest compared to the lowest concentration tested; fs= factor of S; f_{EC}= multiplication or division factor for obtainin 95 % confidential intervals of EC

Tab. 3.3.3: The mean EC levels for Eurycoma-2 with the 95 % confidential intervals

EC	Mean	95% Confidence Intervals Lower	Higher
EC_1	0,0066	0,0004	0,1102
EC_{16}	0,5120	0,2483	1,0556
EC_{50}	13,2333	6,4183	27,2846
EC_{84}	342,0396	165,8927	705,2212
EC_{90}	874,6235	164,2994	4655,9276
EC_{95}	2869,3704	371,0410	22189,6932
EC_{99}	26639,3512	1588,8045	446659,7438

In the table 3.3.3 you can see the different means of EC which show the effective doses. The mean of the EC 50 was 13,2333, of the EC 90 was 874,6235 and of the EC 99 was 26639,3512. The unit of the means of EC is nmol/l.

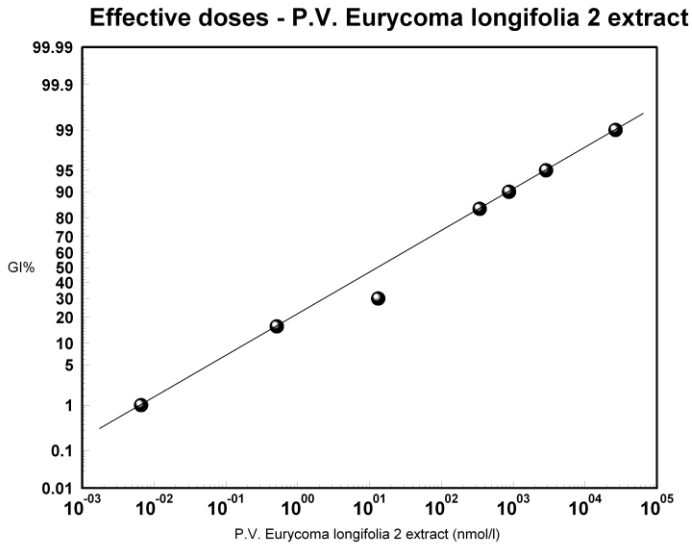

Fig. 3.3.1: The log-probit regression for eurycoma longifolia 2

From the means of the EC´s as shown in the Fig. 3.3.1 the log-probit regression of the effective doses of the eurycoma longifolia 2 extract are visible.

3. 4 Eurycoma longifolia 3

The valid results have shown the following values.
The number of the isolates with valid results are 31. There isolates were utilized for the in vitro test.

Tab. 3.4.1: The drug concentration in nmol/l of Eurycoma-3 and the inhibition of the schizonts maturation (SMI) in percent.

Drug conc.	SMI%
3,0	28,63
10,0	48,17
30,0	62,73
100,0	74,07
300,0	83,61
1000,0	91,76
3000,0	95,39

At the drug concentration of 3 nmol/l to 3000 nmol/l a maturation inhibition of the schizonts from 28,63 % to 95,39% was observed.

Tab. 3.4.2: The regression parameters[4] for Eurycoma-3

n =	31	S =	21,9787	f_s =	3,2233
a =	4,1627	A =	4,5746	f_{EC-50} =	2,1569
b =	0,3218	K =	7	f_{EC-90} =	5,4995
r =	0,9971	N' =	124	f_{EC-95} =	7,9926
χ^2 =	0,2810	R =	1000	f_{EC-99} =	17,3890

Table 3.4.2 informs about regression parameters.

The regression parameters show the following interesting results. One important point is the slope function which was 21,9787. The value of the correlation of regression was in this study, with an result of 0,9971 relatively high, because it was more than 0,97. Another point is χ^2 were you can see the heterogeneity. In this study it was relatively low, because the result was 0,9971. The factor of the slope function was 3,2233. The factors of EC´s shows the following values: The f_{EC}– 50 was 2,1569, the f_{EC}-90 was 5,4995, the f_{EC}–95 was 7,9926 and the f_{EC}–99 was 17,3890.

[4] From Litchfield & Wilcoxon (1949): n= number of isolate; a= intercept of regression; b= slope of regression; r= correlation of regression; χ^2= heterogeneity; S= slope function; A= intermediate term for fS; K= number of drug concentrations; N´= number of points from EC 16 to EC84; R= factor of the highest compared to the lowest concentration tested; fs= factor of S; f_{EC}= multiplication or division factor for obtainin 95 % confidential intervals of EC

Table 3.4.3: The mean EC levels for Eurycoma-3 with the 95 % confidential intervals

EC	Mean	95% Confidence Intervals Lower	Higher
EC_1	0,0098	0,0006	0,1702
EC_{16}	0,6136	0,2845	1,3235
EC_{50}	13,4869	6,2529	29,0897
EC_{84}	296,4242	137,4315	639,3536
EC_{90}	723,3245	131,5244	3977,9580
EC_{95}	2236,5511	279,8263	17875,9519
EC_{99}	18581,3021	1068,5650	323110,6955

In the table 3.4.3 you can see the different means of EC which show you the effective doses. The mean of the EC 50 was 13,4869, of the EC 90 was 723,3245 and of the EC 99 was 18581,3021.The unit of the means of EC is nmol/l.

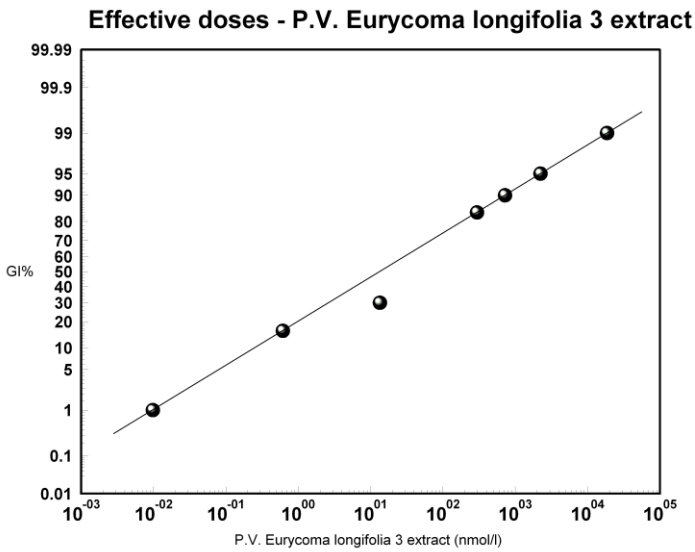

Fig. 3.4.1: The log-probit regression for Eurycoma longifolia 3 extract

From the means of the EC´s it arose in the Fig. 3.4.1 the log-probit regression of the effective doses of the eurycoma longifolia 3 extract are shown.

3. 5 Eurycoma longifolia 1 - Artemisinin

The valid results have shown the following values.
The number of valid isolates was 31. These isolates were utilized for the in vitro test.

Tab. 3.5.1: The drug concentration in nmol/l of Eurycoma longifolia 1 – Artemisinin and the inhibition of the schizonts maturation (SMI) in percent.

Drug conc.	SMI%
3,0	30,21
10,0	46,22
30,0	57,47
100,0	67,37
300,0	74,80
1000,0	85,31
3000,0	89,32

At the drug concentration of 3 nmol/l to 3000 nmol/l a maturation inhibition of the schizonts from 30,21 % to 89,32 % was observed.

Tab. 3.5.2: The regression parameters[5] for Eurycoma longifolia 1 - Artemisinin

n =	31	S =	52,1117	f_S =	5,5483
a =	4,2780	A =	12,0472	f_{EC-50} =	2,4099
b =	0,2516	K =	7	f_{EC-90} =	10,9673
r =	0,9962	N' =	155	f_{EC-95} =	19,3159
χ^2 =	0,2787	R =	1000	f_{EC-99} =	61,6615

Table 3.5.2 refers to the regression parameters.

The regression parameters show the following interesting results. One important point is the slope function which was 52,1117. The value of the correlation of regression was in this study with an result of 0,9962 relatively high, because it was more than 0,97. Another point is χ^2 were you can see the heterogeneity. In this study it was relatively low, because the result was 0,2787. The factor of the slope function was 5,5483. The factors of EC´s shows the following values: The f_{EC}– 50 was 2,4099, the f_{EC}-90 was 10,9673, the f_{EC}–95 was 19,3159 and the f_{EC}–99 was 61,6615.

[5] From Litchfield & Wilcoxon (1949): n= number of isolate; a= intercept of regression; b= slope of regression; r= correlation of regression; χ^2= heterogeneity; S= slope function; A= intermediate term for fS; K= number of drug concentrations; N´= number of points from EC 16 to EC84; R= factor of the highest compared to the lowest concentration tested; fs= factor of S; f_{EC}= multiplication or division factor for obtainin 95 % confidential intervals of EC

Tab. 3.5.3: The mean EC levels for Eurycoma longifolia 1 – Artemisinin with the 95 % confidential intervals

EC	Mean	95% Confidence Intervals Lower	Higher
EC_1	0,0017	0,0000	0,1048
EC_{16}	0,3385	0,1404	0,8157
EC_{50}	17,6378	7,3188	42,5058
EC_{84}	919,1364	381,3959	2215,0520
EC_{90}	2877,6518	262,3848	31560,0537
EC_{95}	12196,9304	631,4437	235595,2145
EC_{99}	183079,8239	2969,1115	11288973,7751

In the table 3.5.3 you can see the different means of EC which show you the effective doses. The mean of the EC 50 was 17,6378, of the EC 90 was 2877,6518 and of the EC 99 was 183079,8239. The unit of the means of EC is nmol/l.

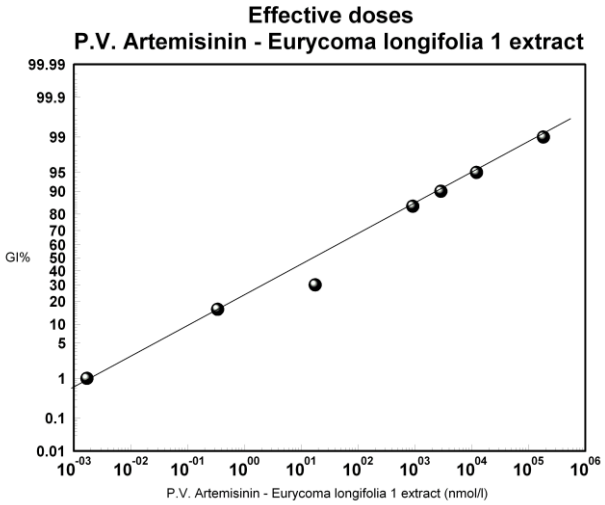

Fig. 3.5.1: The log-probit regression for Eurycoma longifolia 1 extract - Artemisinin

From the means of the EC´s it arose in the Fig. 3.5.1 the log-probit regression of the effective doses of the eurycoma longifolia 1 extract - artemisinin.

3. 6 Eurycoma longifolia 2 - Artemisinin

The valid results have shown the following values.
The number of valid isolates was 31. This isolates were suitable for the in vitro test.

Tab. 3.6.1: The drug concentration in nmol/l of Eurycoma-2 – Artemisinin and the resulting inhibition of the schizonts maturation (SMI) in percent.

Drug conc.	SMI%
3,0	32,41
10,0	51,07
30,0	64,79
100,0	74,67
300,0	83,03
1000,0	89,54
3000,0	92,48

At the drug concentration of 3 nmol/l to 3000 nmol/l a maturation inhibition of the schizonts from 32,41 % to 92,48 % was observed.

Tab. 3.6.2: The regression parameters[6] for Eurycoma-2 - Artemisinin

n =	31	S =	36,2030	f_s =	4,1054
a =	4,3517	A =	7,7783	f_{EC-50} =	2,2223
b =	0,2771	K =	7	f_{EC-90} =	7,4048
r =	0,9926	N' =	155	f_{EC-95} =	11,7436
χ^2 =	0,6031	R =	1000	f_{EC-99} =	30,3745

In table 3.6.2 are the regression parameters summarized.

The regression parameters show the following interesting results. One important point is the slope function which was 36,2030. The value of the correlation of regression was in this study with an result of 0,9926 relatively high, because it was more than 0,97. Another point is χ^2 were you can see the heterogeneity. In this study it was relatively low, because the result was 0,6031. The factor of the slope function was 4,1054. The factors of EC´s shows the following values: The f_{EC}– 50 was 2,2223, the f_{EC}-90 was 7,4048, the f_{EC}–95 was 11,7436 and the f_{EC}–99 was 30,3745.

[6] From Litchfield & Wilcoxon (1949): n= number of isolate; a= intercept of regression; b= slope of regression; r= correlation of regression; χ^2= heterogeneity; S= slope function; A= intermediate term for fS; K= number of drug concentrations; N´= number of points from EC 16 to EC84; R= factor of the highest compared to the lowest concentration tested; fs= factor of S; f_{EC}= multiplication or division factor for obtainin 95 % confidential intervals of EC

Tab. 3.6.3: The mean EC levels for Eurycoma-2 - Artemisinin with the 95 % confidential intervals

EC	Mean	95% Confidence Intervals Lower	Higher
EC_1	0,0023	0,0001	0,0712
EC_{16}	0,2866	0,1290	0,6370
EC_{50}	10,3768	4,6693	23,0606
EC_{84}	375,6715	169,0443	834,8646
EC_{90}	1058,7630	142,9837	7839,9101
EC_{95}	3928,4615	334,5185	46134,3932
EC_{99}	45943,6076	1512,5712	1395514,5014

In the table 3.6.3 you can see the different means of EC which show the effective doses. The mean of the EC 50 was 10,3768, of the EC 90 was 1058,7630 and of the EC 99 was 45943,6076. The unit of the means of EC is nmol/l.

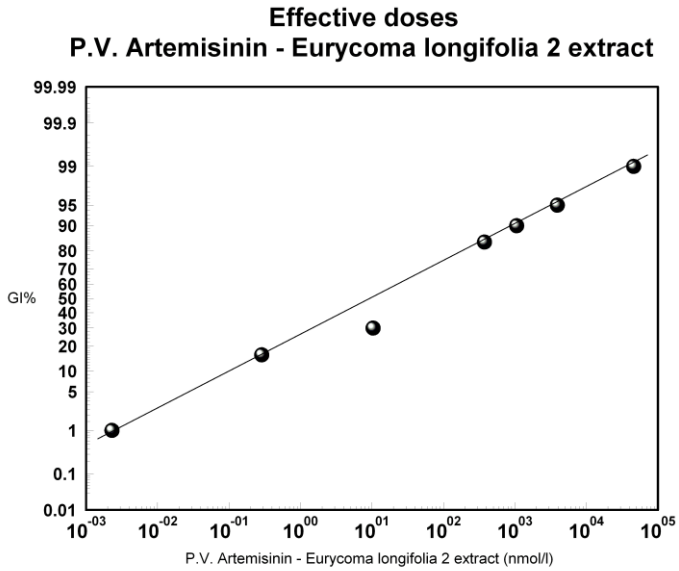

Fig. 3.6.1: The log-probit regression for Eurycoma longifolia 2 extract - Artemisinin

From the means of the EC´s it arose in the Fig. 3.6.1 the log-probit regression of the effective doses of the eurycoma longifolia 3 extract – artemisinin are followed through.

3. 7 Eurycoma longifolia 3 - Artemisinin

The valid results have shown the following results.
The number of valid isolates was 31. This isolates were suitable for the in vitro test.

Table 3.7.1: The drug concentration in nmol/l of Eurycoma longifolia 3 – Artemisinin and the resulting inhibition of the schizonts maturation (SMI) in percent.

Drug conc.	SMI%
3,0	32,73
10,0	52,66
30,0	65,70
100,0	73,19
300,0	81,45
1000,0	87,99
3000,0	90,74

At the drug concentration of 3 nmol/l to 3000 nmol/l a maturation inhibition of the schizonts from 32,73 % to 90,74 % has been observed.

Tab. 3.7.2: The regression parameters[7] for Eurycoma longifolia 3 – Artemisinin

n =	31	S =	49,8116	f_S =	5,3366
a =	4,4210	A =	11,3852	f_{EC-50} =	2,3858
b =	0,2545	K =	7	f_{EC-90} =	10,4249
r =	0,9871	N' =	155	f_{EC-95} =	18,1136
χ^2 =	0,9485	R =	1000	f_{EC-99} =	56,2722

In table 3.7.2 the regression parameter are listed.

The regression parameters show the following interesting results. One important point is the slope function which was 49,8116. The value of the correlation of regression was 0,9871. It was relatively high, because the result was higher than 0,97. Another point is χ^2 were you can see the heterogeneity. In this study it was 0,9485. This was relatively low. The slope function was 49,8116. The factor of the slope function was 5,3366. The factors of EC´s shows the following values: The f_{EC}– 50 was 2,3858, the f_{EC}-90 was 10,4249, the f_{EC}–95 was 18,1136 and the f_{EC}–99 was 56,2722.

[7] From Litchfield & Wilcoxon (1949): n= number of isolate; a= intercept of regression; b= slope of regression; r= correlation of regression; χ^2= heterogeneity; S= slope function; A= intermediate term for fS; K= number of drug concentrations; N´= number of points from EC 16 to EC84; R= factor of the highest compared to the lowest concentration tested; fs= factor of S; f_{EC}= multiplication or division factor for obtainin 95 % confidential intervals of EC

Tab. 3.7.3: The mean EC levels for Eurycoma longifolia 3 - Artemisinin with 95 % confidential intervals

EC	Mean	95% Confidence Intervals Lower	Higher
EC_1	0,0010	0,0000	0,0586
EC_{16}	0,1954	0,0819	0,4662
EC_{50}	9,7330	4,0795	23,2214
EC_{84}	484,8164	203,2054	1156,6963
EC_{90}	1498,2211	143,7150	15618,8738
EC_{95}	6246,3502	344,8432	113143,8500
EC_{99}	90904,1172	1615,4359	5115373,7265

Table 3.7.3 refers to the different means of EC which based on the effective doses. The mean of the EC 50 was 9,7330, of the EC 90 was 1498,2211 and of the EC 99 was 90904,1172. The unit of the means of EC is nmol/l.

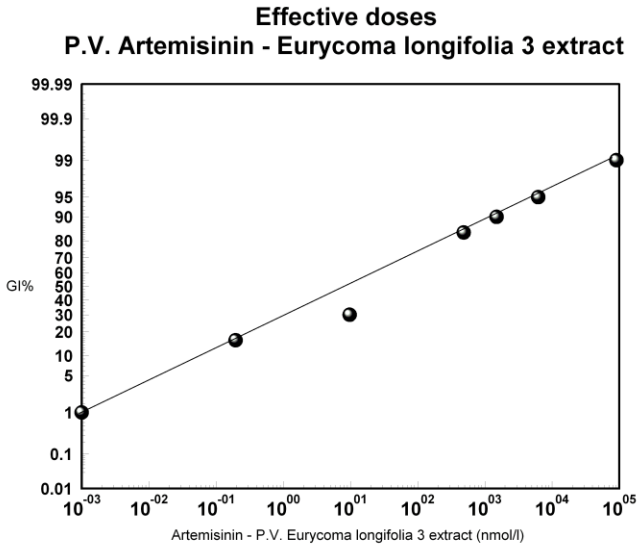

Fig. 3.7.1: The log-probit regression for eurycoma longifolia 3 - artemisinin

From the means of the EC´s it arose in the Fig. 3.7.1 the log-probit regression of the effective doses of the eurycoma longifolia 3 – artemisinin are reproduced.

3. 8 Variance analysis of resulting data

In the book from Swaroop et al. they wrote about statistical methods, which I needed for the evaluation [60]. Variance analysis was introduced since the mixture of the artemisinin and the parallel administered eurycomanon charges resulted in *Plasmodium vivax* always in a significantly lower antiplamodiual activity as compared to freshly prepared 0,5 artemisinin: 0,5 eurycomanon charges. This indicates that the artemisinin + eurycomanon charge prepared at the Institute of Specific Prophylaxis and Tropical Medicine, Medical University of Vienna, has lost part of its activity due to long contact between aremisinin and the eurycomanon. This was obviously due to unstable artemisinin in the mixture. At the same time, the comparison between the two formulations indicated synergism at the lower artemisinin and eurycoma charges [60].

The term is the probability that the difference is merely due to chance [60].

$$t = \frac{x1 - x2}{\sqrt{(v1 + v2) * {}^{1}/_{\eta}}}$$

x1 and x2 denoting the difference of the incidences, 2n the double of cases incorporated in the analysis, and v1 as well as v2 the variances between the two sets of figures [60].

Analysis

EURY1 – ART at IC_{50}

Result: 91,9466 Degrees of Freedom 54 (= 2,6908 at p = 0,01) significant synergism

EURY2 – ART at IC_{50}

Result: 37,2177 Degrees of Freedom 56 (= 2,6952 at p = 0,01) significant synergism

EURY3 – ART at IC_{50}

Result: 93,2021 Degrees of Freedom 52 (= 2,6864 at p = 0,01) significant Synergism

EURY1 – ART at IC_{90}

Result: 32,1322 Degrees of Freedom 52 (= 2,6864 at p = 0,1) significant synergism

EURY2 – ART at IC_{90}

Result: 41,3496 Degrees of Freedom 56 (= 2,6952 at p = 0,1) significant synergism

EURY3 – ART at IC_{90}

Result: 29,7526 Degrees of Freedom 52 (= 2,6864 at p = 0,1) significant Synergism

4. Discussion

In all the seven studies, which included the study of Artemisinin, of eurycoma longifolia 1, of eurycoma longifolia 2 , of eurycoma longifolia 3, of eurycoma longifolia 1 – artemisinin, of eurycoma longifolia 2 – artemisinin and of eurycoma longifolia 3 – artemisinin it was seen, that the drugs shows an effect against the malaria parasite *Plasmodium vivax*.

But the real essential statement is, that we found out, that there is a significant synergism between eurycoma longifolia 1 – artemisinin at IC 50; eurycoma longifolia 2 – artemisinin at IC 50; eurycoma longifolia 3 – artemisinin at IC 50; eurycoma longifolia 1 – artemisinin at IC 90; eurycoma longifolia 2 – artemisinin at IC 90 and eurycoma longifolia 3 – artemisinin at IC 90.

It was also observed that the effect of the straight combination acted more rapidly.

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6. Appendix

6. 1 Zusammenfassung / Abstract

Zusammenfassung:

Malaria ist eine klinisch manifeste Infektion und daher ist es von essentieller Bedeutung sowohl eine Kontrolle des Vektors zum einen und zum anderen ausreichende Behandlungsmöglichkeiten zu finden.

Da man mit dem großen Problem der Resistenzentwicklung des Parasiten gegen die pharmakologischen Therapeutika zu kämpfen hat, ist es von Bedeutung dem so gut wie möglich durch die Forschung entgegenzuwirken.

In dieser Studie soll die pharmakokinetische Interaktion zwischen Artemisinin und den 3 standardisierten Eurycoma longifolia Extrakten bei Plasmodium vivax herausgefunden werden.

Mae Sot ist jenes Gebiet, wo diese Studien durchgeführt wurden. Dabei hatten wir 47 Patienten, welche teils in Myanmar und zum anderen Teil in Thailand infiziert wurden.

Es wurde eine in vitro Prüfung durchgeführt.

Mit Hilfe der log-probit Analyse kamen wir zu folgenden wichtigen EC Werten:

Für Artemisinin erhielten wir für EC-50 den Wert 18,8001 nM, für EC-90 den Wert 451,8291 nM und für EC-99 den Wert 6033,2202 nM.

Für Eurycoma longifolia 1 erhielten wir für EC-50 den Wert 16,7812 nM, für EC-90 den Wert 988,2038 nM und für EC-99 den Wert 27396,0087 nM.

Für Eurycoma longifolia 2 erhielten wir für EC-50 den Wert 13,2333 nM, für EC-90 den Wert 874,6235 nM und für EC-99 den Wert 26639,3512 nM.

Für Eurycoma longifolia 3 erhielten wir für EC-50 den Wert 13,4869 nM, für EC-90 den Wert 723,3245 nM und für EC-99 den Wert 18581,3021 nM.

Für Eurycoma longifolia 1 – Artemisinin erhielten wir für EC-50 den Wert 17,6378 nM, für EC-90 den Wert 2877,6518 nM und für den Wert EC-99 den Wert 183079,8239 nM.

Für Eurycoma longifolia 2 – Artemisinin erhielten wir für EC-50 den Wert 10,3768, für EC-90 den Wert 1058,7630 nM und für den Wert 45943,6076 nM.

Für Eurycoma longifolia 3 – Artemisinin erhielten wir für EC-50 den Wert 9,7330 nM, für EC-90 den Wert 1498,2211 nM und für EC-99 den Wert 90904,1172 nM.

Durch die anschließende Varianzanalyse konnte man einen Synergismus zwischen den Eurycoma longifolia Extrakten mit Artemisinin bei jeweils IC-50 und bei IC-90 feststellen.

Abstract

Malaria is a clinically manifest infection and for this it is essential to make a control of the vector and a adequate treatment.

Because a big problem of this is, that the resistance pressure against the pharmacologic therapeutic is big. So it is essential to make a good research.

In this study I will show you the pharmacokinetic interaction between artemisinin and the 3 standardized formulations of eurycoma longifolia extracts at *Plasmodium vivax.*

The study was realized in Mae Sot. There were 47 patients. They were infected at one part in Myanmar and at the other part in Thailand.

In this study we have done a in vitro test.

With the help of the log-probit analysis we got the following important EC values:

For artemisinin the EC-50 was 18,8001 nM, the EC-90 was 451,8292 nM and the EC-99 was 6033,2202 nM.

For eurycoma longifolia 1 the EC-50 was 16,7812 nM, the EC-90 was 988,2038 nM and the EC-99 was 27396,0087 nM.

For eurycoma longifolia 2 the EC-50 was 13,2333 nM, the EC-90 was 874,6235 nM and the EC-99 was 26639,3512 nM.

For eurycoma longifolia 3 the EC-50 was 13,4869 nM, the EC-90 was 723,3245 nM and the EC-99 was 18581,3021 nM.

For eurycoma longifolia 1 – artemisinin the EC-50 was 17,6378 nM, the EC-90 was 2877,6518 nM and the EC-99 was 183079,8239 nM.

For eurycoma longifolia 2 – artemisinin the EC-50 was 10,3768 nM, the EC-90 was 1058,7630 nM and the EC-99 was 45943,6076 nM.

For eurycoma longifolia 3 – artemisinin the EC-50 was 9,7330 nM, the EC-90 was 1498,2211 nM and the EC-99 was 90904,1172 nM.

Through the following varianz analysis, we could saw a synergism between eurycoma longifolia extracts with artemisinin at IC-50 and the same at IC-90.

6. 2 Tables

Tab. 1.3.1: The most malaria pathogens for the humans and their characteristics.
Source: Malaria (Wernsdorfer W. H. & Wernsdorfer G., 2010)

Tab. 1.5.1: The 29 species of Anopheles which are singnificant vectors of malaria.
Source: Malaria (Wernsdorfer W. H. & Wernsdorfer G., 2010)

Tab. 3.1.1: The drug concentration in nmol/l of Artemisin and the inhibition of the schizonts maturation (SMI) in percent.

Tab. 3.1.2: The regression parameters for Artemisinin

Tab. 3.1.3: The mean EC levels for Artemisinin and the 95 % confidential intervals

Tab. 3.2.1: The drug concentration in nmol/l of Eurycoma-1 and the inhibition of the schizonts maturation (SMI) in percent.

Tab. 3.2.2: The regression parameters for Eurycoma-1

Tab. 3.2.3: The mean EC levels for Eurycoma-1 with the 95 % confidential intervals

Table 3.3.1: The drug concentration in nmol/l of Eurycoma-2 and the inhibition of the schizonts maturation (SMI) in percent.

Tab. 3.3.2: The regression parameters for Eurycoma-2

Table 3.3.3: The mean EC levels for Eurycoma-2 with the 95 % confidential Intervals

Tab. 3.4.1: The drug concentration in nmol/l of Eurycoma-3 and the inhibition of the schizonts maturation (SMI) in percent.

Tab. 3.4.2: The regression parameters for Eurycoma-3

Tab. 3.4.3: The mean EC levels for Eurycoma-3 with the 95 % confidential intervals

Tab. 3.5.1: The drug concentration in nmol/l of Eurycoma longifolia 1 – Artemisinin and the inhibition of the schizonts maturation (SMI) in percent.

Tab. 3.5.2: The regression parameters for Eurycoma longifolia 1- Artemisinin

Tab. 3.5.3: The mean EC levels for Eurycoma longifolia 1 –Artemisinin with the 95 % confidential intervals

Tab. 3.6.1: The drug concentration in nmol/l of Eurycoma-2 – Artemisinin and the resulting inhibition of the schizonts maturation (SMI) in percent.

Tab. 3.6.2: The regression parameters for Eurycoma-2 – Artemisinin

Tab. 3.6.3: The mean EC levels for Eurycoma-2 - Artemisinin with the 95 % confidential intervals

Tab. 3.7.1: The drug concentration in nmol/l of Eurycoma longifolia 3 – Artemisinin and the resulting inhibition of the schizonts maturation (SMI) in percent.

Tab. 3.7.2: The regression parameters for Eurycoma longifolia 3 – Artemisinin

Tab. 3.7.3: The mean EC levels for Eurycoma longifolia 3 - Artemisinin with 95 % confidential intervals

6. 3 Figures

Fig. 1.2.1: Areas of the malaria transmission (WHO 2011)

Source: http://www.fam.at/pdf/rel/FAM-Info_MalariaUpdate2011.pdf

(13.03.2012)

Fig. 1.4.1: The life cycle of Plasmodium

Source: http://hardinmd.lib.uiowa.edu/pictures22/cdc/PHIL_3405_lores.jpg

(13.03.2012)

Fig. 2. 1. 1. 1: Structural formulae of artemisinin

Source: Preparation of molecularly imprinted polymers for artemisinin based on the surface of silica gel (Gong & Cao, 2011)

Fig. 2.1.2.1: Structural formulae of the major quassinoids in the standardizided

Eurycoma longifolia extract:

1 = eurycomanone

2 = 13,21 –dihydroeurycomanone

3 = 13α(21)-epoxyeurycomanone

Source: Activitiy of Eurycoma longifolia root extract against Plasmodium

falciparum in Vitro (Wernsdorfer et al., 2009)

Fig. 3.1.1: The log-probit regression for Artemisinin

Fig. 3.2.1: The log-probit regressionfor eurycoma-1

Fig. 3.3.1: The log-probit regression for eurycoma longifolia 2

Fig. 3.4.1: The log-probit regression for Eurycoma longifolia 3

Fig. 3.5.1: The log-probit regression for Eurycoma longifolia 1 extract - Artemisinin

Fig. 3.6.1: The log-probit regression for Eurycoma longifolia 2 extract- Artemisinin

Fig. 3.7.1: The log-probit regression for Eurycoma longifolia 3 - Artemisinin

6. 4 Forms

- Probit calculus sheet for Artemisinin
- Probit calculus sheet for Eurycoma 1
- Probit calculus sheet for Eurycoma 2
- Probit calculus sheet for Eurycoma 3
- Probit calculus sheet for Eurycoma-1 – Artemisinin
- Probit calculus sheet for Eurycoma-2 – Artemisnin
- Probit calculus sheet for Eurycoma-3 – Artemisinin
- VARIANCE ANALYSIS OF RESULTING DATA
- Patients list

Study Area:	Year:	Drug:
MAE SOT	2010	ARTEMISININ PV

	A	B	C	D	E	F	G	H
Pat. No.:	Control SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ
	0	3	10	30	100	300	1000	3000
1	100	97,44	84,54	78,25	81,83	45,74	28,68	9,8
7	100	78,93	49,59	37,19	0	0	0	0
10	100	81,37	79,05	41,21	25,84	14,9	0	0
11	100	86,41	81,15	58,26	25,7	18,73	10,16	0
12	100	98,43	53,24	17,88	5,7	0	0	0
14	100	90,73	63,64	36,9	29,41	4,81	0	0
15	100	61,39	55,56	32,86	24,76	7,25	0	0
16	100	98,46	65,16	49,68	34,84	22,95	11,37	3,47
19	100	88,56	51,2	32,58	12,5	7,18	0	0
22	100	95	65,12	52,32	36,46	22,44	14,88	0
23	100	74,41	59,65	45,67	25,98	8,76	2,95	0
24	100	88,44	60,99	42,21	26,73	16,72	0	0
25	100	84,72	66,31	47,99	42	20,02	7,42	3,84
26	100	74,76	60,86	47,37	35,63	29,69	0	0
27	100	75,08	64,58	50,25	39,86	38,04	28,36	15,44
28	100	66,56	31,35	26,85	3,22	0	0	0
29	100	77,49	66,84	27,59	23,29	13,42	1,39	0
30	100	85,08	55,86	49,59	42,66	10,48	8,63	0,74
31	100	91,57	69,26	68,74	40,47	18,42	1,45	0,13
33	100	83,14	36,86	25,59	0	0	0	0
34	100	78,58	56,56	39,67	27,45	4,98	0	0
35	100	76,18	36,03	28,55	15,73	0	0	0
36	100	66,61	60,03	40,46	28,29	12,66	0	0
37	100	64,09	43,54	40,07	16,06	0	0	0
38	100	82,31	57,42	49,26	34	36,55	20,02	16,95
40	100	84,65	57,46	46,06	16,9	7,61	4,65	0
41	100	40,14	35,68	10,79	7,76	0	0	0
43	100	72,41	65,55	62,2	49,36	40,83	25,52	24,4
46	100	70,1	35,66	15,56	0	0	0	0
47	100	81,99	35,5	19,03	0,02	0	0	0

Study Area:	Year:	Drug:
MAE SOT	2010	ARTEMISININ PV

Drug conc.	SMI%
3,0	20,17
10,0	43,19
30,0	59,31
100,0	74,92
300,0	86,59
1000,0	94,48
3000,0	97,51

n =	30	S =	11,7893	f_s =	2,1350
a =	3,8174	A =	2,6361	f_{EC-50} =	1,8661
b =	0,4031	K =	7	f_{EC-90} =	3,2116
r =	0,9971	N' =	120	f_{EC-95} =	4,0484
χ^2 =	0,3481	R =	1000	f_{EC-99} =	6,6087

EC	Mean	95% Confidence Intervals Lower	Higher
EC_1	0,0586	0,0089	0,3872
EC_{16}	1,5947	0,8545	2,9759
EC_{50}	18,8001	10,0744	35,0834
EC_{84}	221,6402	118,7698	413,6097
EC_{90}	451,8291	140,6855	1451,1054
EC_{95}	1112,7533	274,8624	4504,8723
EC_{99}	6033,2202	912,9270	39871,4745

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Study Area:	Year:	Drug:
MAE SOT	2010	PV-EURY-1

	A	B	C	D	E	F	G	H
Pat. No.:	Control SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ
	0	3	10	30	100	300	1000	3000
1	100	82,24	65,38	55,86	49,1	15,31	4,83	1,52
7	100	68,65	56,92	43,65	20,77	10,38	7,31	5,75
10	100	81,14	64,91	42,72	33,84	23,72	6,38	1,72
11	100	83,93	69,81	56,01	25	15,42	19,97	12,32
12	100	63,26	50,26	34,14	24,61	10,75	5,55	2,87
14	100	65,03	55,33	35,25	31,56	20,36	4,23	0
15	100	68,22	49,56	39,97	31,15	16,39	4,04	0
16	100	71,91	55,77	21,56	30,88	20,31	11,13	6,1
19	100	72,16	37,61	31,34	23,62	11,08	4,37	1,72
22	100	70,04	48,31	39,21	21,29	14,98	7,78	4,04
23	100	72,41	57,26	33,58	25,64	22,34	12,21	6,67
24	100	59,31	46,56	38,14	32,4	16,58	10,2	6,28
25	100	106,05	83,18	62,19	47,64	32,7	16,45	8,28
26	100	75,54	67,54	47,08	36,46	19,38	15,69	12,76
27	100	88,13	73,29	52,67	30,71	19,58	11,42	6,66
28	100	72,72	52,1	40,74	35,06	13,58	9,88	7,79
29	100	62,59	45,47	38,79	31,49	23,68	14,61	9,08
30	100	67,07	47,56	36,31	14,36	7,45	2,17	0
31	100	72,12	44,6	36,89	27,4	17,79	10,44	6,73
33	100	58,63	44,07	37,11	20,23	15,72	9,28	5,48
34	100	69,39	46,39	41,31	34,09	19,12	5,21	1,92
35	100	58,37	47,49	37,8	29,31	19,74	9,69	4,76
36	100	70,56	62,63	46,37	37,37	22,18	12,9	7,5
37	100	71,15	46,07	40,33	35,41	11,97	5,08	2,16
35	100	66,38	56,78	46,31	31,56	19,55	5,32	1,45
38	100	68,23	54,73	47,18	30,18	15,83	6,48	2,65
40	100	61,87	39,37	32,65	24,69	13,85	9,74	6,84
41	100	65,56	53,17	43,23	34,01	23,63	11,53	5,63
43	100	73,38	66,67	60,51	44,18	20,36	10,4	5,37
46	100	64,07	52,15	36,57	23,37	15,1	11,45	8,68
47	100	81,27	63,06	55,15	30,41	21,13	17,7	14,83

Study Area:	Year:	Drug:
MAE SOT	2010	PV-EURY-1

Drug conc.	SMI%
3,0	28,67
10,0	45,03
30,0	57,72
100,0	69,43
300,0	82,26
1000,0	90,53
3000,0	94,59

n =	31	S =	23,6325	f_s =	2,9939
a =	4,1132	A =	4,9173	f_{EC-50} =	2,0211
b =	0,3145	K =	7	f_{EC-90} =	4,9025
r =	0,9988	N' =	155	f_{EC-95} =	6,9682
c_ =	0,1095	R =	1000	f_{EC-99} =	14,4586

EC	Mean	95% Confidence Intervals Lower	Higher
EC_1	0,0103	0,0007	0,1486
EC_{16}	0,7101	0,3513	1,4352
EC_{50}	16,7812	8,3029	33,9169
EC_{84}	396,5803	196,2170	801,5409
EC_{90}	988,2038	201,5699	4844,7043
EC_{95}	3137,6327	450,2788	21863,6507
EC_{99}	27396,0087	1894,7884	396108,2335

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Study Area:	Year:	Drug:
MAE SOT	2010	PV-EURY-2

	A	B	C	D	E	F	G	H
Pat. No.:	Control SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ
	0	3	10	30	100	300	1000	3000
1	100	68,51	49,85	39,1	28,66	18,81	11,49	7,07
7	100	66,78	44,3	30,2	16,95	9,23	6,71	4,88
10	100	60,11	58,05	56,55	44,57	41,01	16,1	6,32
11	100	52,22	46,84	33,51	19,25	9,56	5,25	2,88
12	100	65,99	52,86	30,3	28,96	10,44	3,87	1,43
14	100	70,65	38,81	28,52	14,93	10,45	5,31	2,65
15	100	68,35	60,13	43,54	32,15	20	8,86	3,42
16	100	81,21	57,1	44,62	32,57	14,92	9,9	6,56
19	100	75,82	59,55	40,3	21,04	18,21	5,67	1,77
22	100	79,45	62,64	45,83	41,1	24,53	14,07	8,07
23	100	71,56	45,87	25	23,28	19,61	7,91	3,79
24	100	69,68	50,06	34,84	32,58	21,64	9,16	3,88
25	100	73,96	43,52	35,07	19,68	15,16	5,32	1,87
26	100	71,9	57,93	37,75	26,51	18,73	8,79	4,13
27	100	65,12	47,2	40,12	25,85	19,15	3,78	0
28	100	70,37	53,19	44,82	38,44	18,61	6,5	2,27
29	100	63,94	49,12	32,79	24,62	15,58	7,91	4,08
30	100	66,51	48,48	40,19	14,04	8,61	2,39	0
31	100	68,12	37,96	29,47	20,3	10,55	8,83	7,39
33	100	66,28	49,59	24,74	21,59	13,07	5,48	2,3
34	100	72,38	56,5	37,4	27,16	19,68	7,83	3,78
35	100	65,76	55,83	41,32	24,19	10,17	4,84	2,3
36	100	59,48	44,56	30,05	28,5	17,93	7,56	3,78
37	100	71,25	62,24	39,65	26,7	15,01	9	5,35
35K	100	68,49	52,34	36,33	28,26	21,74	18,23	15,29
38	100	69,31	47,38	41,17	35,32	21,92	11,33	5,86
40	100	79,79	68,35	47,4	27,79	24,96	13,97	7,88
41	100	75,62	59,56	38,37	18,14	18,14	11,63	7,46
43	100	66,75	47,66	36,75	32,21	21,69	13,51	8,47
46	100	66,05	54,43	44,65	32,1	21,93	14,13	9,7
47	100	70,65	60,07	43,17	35,32	28,16	13,48	6,45

Study Area:	Year:	Drug:
MAE SOT	2010	PV-EURY-2

Drug conc.	SMI%
3,0	30,90
10,0	47,68
30,0	62,14
100,0	72,81
300,0	81,96
1000,0	91,01
3000,0	95,13

n =	31	S =	25,8468	f_s =	3,1885
a =	4,2102	A =	5,3884	f_{EC-50} =	2,0618
b =	0,3058	K =	7	f_{EC-90} =	5,3234
r =	0,9983	N' =	155	f_{EC-95} =	7,7333
χ^2 =	0,1474	R =	1000	f_{EC-99} =	16,7669

EC	Mean	95% Confidence Intervals Lower	Higher
EC_1	0,0066	0,0004	0,1102
EC_{16}	0,5120	0,2483	1,0556
EC_{50}	13,2333	6,4183	27,2846
EC_{84}	342,0396	165,8927	705,2212
EC_{90}	874,6235	164,2994	4655,9276
EC_{95}	2869,3704	371,0410	22189,6932
EC_{99}	26639,3512	1588,8045	446659,7438

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Study Area:	Year:	Drug:
MAE SOT	2010	PV-EURY-3

	A	B	C	D	E	F	G	H
Pat. No.:	Control SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ
	0	3	10	30	100	300	1000	3000
1	100	108,7	39,78	31,35	20,17	18,09	14,92	12,3
7	100	79,39	46,67	28,28	21,21	6,87	0	0
10	100	77,53	57,87	44,72	37,42	24,38	6,07	1,51
11	100	81,52	65	46,36	41,52	28,64	12,88	5,79
12	100	49,22	37,66	31,67	16,55	12,13	2,28	0
14	100	69,18	50,39	37,9	25,12	13,41	6,01	2,69
15	100	67,09	53,7	37,37	21,94	13,65	5,87	2,52
16	100	65,2	47,9	28,76	17,5	12,79	9,62	7,24
19	100	66,57	44,43	31,88	19,04	10,44	5,08	2,47
22	100	69,97	52,27	34,92	28,64	18,16	11,87	7,76
23	100	70,4	47,09	32,46	22,17	13,37	8	4,79
24	100	69,3	46,5	36,79	26,94	13,99	7,9	4,46
25	100	77,07	63,2	50	41,39	32,77	18,68	10,65
26	100	76	41,91	30,43	24,52	15,13	10,96	7,93
27	100	79,17	67,16	41,39	36,32	30,31	13,48	5,95
28	100	74,13	59,51	45,28	28,46	9,83	4,01	1,64
29	100	67,31	47,66	44,64	33,24	16,21	11,81	8,6
30	100	77,46	65,9	40,03	22,4	16,62	4,34	0
31	100	68,47	42,14	33,98	16,84	12,04	6,22	3,21
33	100	57,63	50,34	34,8	20,63	16,23	10,45	6,73
34	100	59,31	51,35	38,73	26,59	12,75	6,99	3,83
35	100	71,5	61,43	46,68	24,69	9,46	7,49	5,93
36	100	81,49	53,95	35,58	25,39	16,64	11,05	7,34
37	100	73,92	60,66	36,21	21,46	10,88	3,43	0
35K	100	74,62	46,52	35,3	18,54	10,04	5,9	3,47
38	100	73,49	68,37	50,85	37,83	25,74	15,97	9,91
40	100	63,13	47,76	28,66	25,37	17,16	11,34	7,49
41	100	67,14	52,04	45,91	37,89	29,56	5,35	0,97
43	100	70,7	42,33	27,22	11,19	8,54	1,73	0
46	100	57,11	44,92	31,06	20,07	10,39	4,78	2,2
47	100	68,9	50,39	36,24	32,66	21,93	11,04	5,56

Study Area:	Year:	Drug:
MAE SOT	2010	PV-EURY-3

Drug conc.	SMI%
3,0	28,63
10,0	48,17
30,0	62,73
100,0	74,07
300,0	83,61
1000,0	91,76
3000,0	95,39

n =	31	S =	21,9787	f_s =	3,2233
a =	4,1627	A =	4,5746	f_{EC-50} =	2,1569
b =	0,3218	K =	7	f_{EC-90} =	5,4995
r =	0,9971	N' =	124	f_{EC-95} =	7,9926
χ^2 =	0,2810	R =	1000	f_{EC-99} =	17,3890

EC	Mean	95% Confidence Intervals	
		Lower	Higher
EC_1	0,0098	0,0006	0,1702
EC_{16}	0,6136	0,2845	1,3235
EC_{50}	13,4869	6,2529	29,0897
EC_{84}	296,4242	137,4315	639,3536
EC_{90}	723,3245	131,5244	3977,9580
EC_{95}	2236,5511	279,8263	17875,9519
EC_{99}	18581,3021	1068,5650	323110,6955

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Study Area:	Year:	Drug:
MAE SOT	2010	PV-EURY-1-ART

	A	B	C	D	E	F	G	H
Pat. No.:	Control SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ
	0	3	10	30	100	300	1000	3000
1	100	68,19	59,86	34,78	28,73	13,45	8,67	5,59
7	100	54,59	37,66	30,45	15,44	5,48	0	0
10	100	55,19	36,96	32,41	28,23	70,76	11,39	6,24
11	100	52,54	23,39	28,81	19,49	5,59	0	0
12	100	59,18	49,77	49,77	7,59	9,1	14,72	10
14	100	68,23	43,92	34,2	28,82	23,44	9,55	3,89
15	100	67,43	60,07	38,46	26,68	15,22	7,86	4,05
16	100	61,99	38,01	31,07	22,24	14,67	4,73	1,53
19	100	56,07	42,58	27,75	24,58	16,31	11,44	8,02
22	100	59,47	48,97	32,08	27,95	19,14	10,32	5,56
23	100	69,51	56,12	41,17	20,78	16,5	7,38	3,3
24	100	63,38	44,71	34,71	28,38	20,15	10,59	5,57
25	100	71,97	59,87	43,95	35,82	24,54	10,12	4,17
26	100	63,15	44,56	39,7	27,97	18,93	14,57	11,21
27	100	87,65	70,15	42,54	34,99	12,86	7,89	4,89
28	100	74,25	53,22	42,07	30,93	22,45	9,26	3,88
29	100	78,82	61,69	48,07	37,38	20,63	16,21	12,74
30	100	64,74	41,06	32,88	25,21	19,42	5,28	1,94
31	100	52,08	43,09	28,79	27,45	13,98	10,82	8,37
33	100	90,32	83,51	82,31	79,4	77,63	71,33	65,57
34	100	77,8	57,76	36,28	33,57	24,01	10,29	4,91
35	100	80,34	60	54,12	38,15	26,89	9,08	3,07
36	100	76,09	61,37	41,98	31,49	9,33	4,52	2,79
37	100	73,6	52,27	37,06	21,12	20,45	7,87	2,53
35	100	87,95	81,69	74,31	70,87	64,21	62,67	61,76
38	100	76,29	69,32	51,32	37,1	30,54	15,06	7,93
40	100	87,63	80,09	75,1	73,7	72,19	69,28	66,99
41	100	73,92	52,4	48,56	37,5	31,01	6,49	1,36
43	100	75	53,48	50,5	38,18	30,1	14,68	7,16
46	100	71,23	54,07	46,13	35,91	22,22	8,23	3,05
47	100	64,94	45,71	27,14	15,84	9,87	4,94	2,97

Study Area:	Year:	Drug:
MAE SOT	2010	PV-EURY-1-ART

Drug conc.	SMI%
3,0	30,21
10,0	46,22
30,0	57,47
100,0	67,37
300,0	74,80
1000,0	85,31
3000,0	89,32

n =	31	S =	52,1117	f_s =	5,5483
a =	4,2780	A =	12,0472	f_{EC-50} =	2,4099
b =	0,2516	K =	7	f_{EC-90} =	10,9673
r =	0,9962	N' =	155	f_{EC-95} =	19,3159
χ^2 =	0,2787	R =	1000	f_{EC-99} =	61,6615

EC	Mean	95% Confidence Intervals Lower	Higher
EC_1	0,0017	0,0000	0,1048
EC_{16}	0,3385	0,1404	0,8157
EC_{50}	17,6378	7,3188	42,5058
EC_{84}	919,1364	381,3959	2215,0520
EC_{90}	2877,6518	262,3848	31560,0537
EC_{95}	12196,9304	631,4437	235595,2145
EC_{99}	183079,8239	2969,1115	11288973,7751

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Study Area:	Year:	Drug:
MAE SOT	2010	PV-EURY-2-ART

	A	B	C	D	E	F	G	H
Pat. No.:	Control SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ
	0	3	10	30	100	300	1000	3000
1	100	70,65	55,97	40,85	26,51	14,35	6,79	3,21
7	100	59,3	32,82	26,74	20,41	6,2	1,03	0
10	100	62,99	42,28	20,71	14,94	4,07	0	0
11	100	66,67	48,72	36,86	29,49	17,34	10,26	6,07
12	100	52,34	37,95	33,09	17,63	4,14	1,26	0
14	100	65,04	44,3	36,44	31,11	20	13,04	8,5
15	100	61,89	49,19	33,06	20,85	6,35	1,3	0
16	100	57,29	33,56	30,85	21,02	18,47	1,19	0
19	100	63,92	45,36	26,8	18,39	10,86	6,83	4,3
22	100	63,23	50,97	32,59	12,86	3,44	1,2	0
23	100	66,27	55,47	50	30,62	25,89	13,91	7,47
24	100	65,64	49,2	18,42	14,96	5,56	2,72	0
25	100	72,28	49,18	25,93	10,43	7	3,43	1,68
26	100	48,91	31,56	19,53	15,94	13,44	8,59	5,49
27	100	70,55	49,64	30,16	21,19	19,06	0	0
28	100	66,31	31,85	24,31	18	17,85	10,62	6,38
29	100	53,99	37,48	14,1	11,32	7,24	4,45	2,74
30	100	71	58,8	33,6	19,97	6,02	3,8	2,4
31	100	71,84	42,33	27,38	27,38	13,59	6,02	2,67
33	100	71	46,68	36,71	20,09	16,62	15,41	14,29
34	100	77,49	54,7	48,2	37,02	19,2	6,22	2,08
35	100	60,61	40,53	33,08	20,08	9,85	4,8	2,33
36	100	83,71	64,22	44,73	30,04	20,96	14,69	10,3
37	100	67,71	47,59	39,24	27,05	16,01	12,18	9,27
35	100	80,13	74,28	72,33	67,66	62,15	59,47	56,9
38	100	73,57	53,87	44,14	40,77	31,67	14,84	6,96
40	100	81,4	54,52	41,6	31,14	23,26	16,15	11,27
41	100	86,06	81,22	70,99	68,6	64,94	60,15	55,77
43	100	70,63	52,38	39,86	20,37	15,52	8,38	4,52
46	100	66,9	50,24	32,14	27,62	19,76	12,98	8,53
47	100	65,93	50,12	27,21	11,74	5,35	2,67	0

Study Area:	Year:	Drug:
MAE SOT	2010	PV-EURY-2-ART

Drug conc.	SMI%
3,0	32,41
10,0	51,07
30,0	64,79
100,0	74,67
300,0	83,03
1000,0	89,54
3000,0	92,48

n =	31	S =	36,2030	f_S =	4,1054
a =	4,3517	A =	7,7783	f_{EC-50} =	2,2223
b =	0,2771	K =	7	f_{EC-90} =	7,4048
r =	0,9926	N' =	155	f_{EC-95} =	11,7436
χ^2 =	0,6031	R =	1000	f_{EC-99} =	30,3745

EC	Mean	95% Confidence Intervals Lower	Higher
EC_1	0,0023	0,0001	0,0712
EC_{16}	0,2866	0,1290	0,6370
EC_{50}	10,3768	4,6693	23,0606
EC_{84}	375,6715	169,0443	834,8646
EC_{90}	1058,7630	142,9837	7839,9101
EC_{95}	3928,4615	334,5185	46134,3932
EC_{99}	45943,6076	1512,5712	1395514,5014

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Study Area:	Year:	Drug:
MAE SOT	2010	PV-EURY-3-ART

	A	B	C	D	E	F	G	H
Pat. No.:	Control SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ	Conc. SCHIZ
	0	3	10	30	100	300	1000	3000
1	100	72,84	45,22	31,3	22,9	14,73	8,06	4,4
7	100	68,02	42,78	31,31	24,56	13,9	0	0
10	100	76,94	47,36	26,25	20	18,89	14,44	11,03
11	100	61,86	30,34	21,06	11,49	7,95	0	0
12	100	54,77	38,15	35,23	26,77	20,77	10,92	5,74
14	100	61,59	45,41	35,77	30,95	18,66	14,93	11,94
15	100	60,32	36,82	23,78	20,34	5,44	3,44	2,8
16	100	57,66	38,7	22,43	21,17	16,27	0	0
19	100	56,91	41,34	23,29	20,96	15,14	15,14	13
22	100	66,76	44,14	26,29	14,99	8,45	4,36	2,24
23	100	50,3	32,16	18,75	12,5	2,29	0	0
24	100	59,31	31,94	20	14,58	9,72	3,33	0
25	100	56,74	41,45	27,85	13,34	12,31	8,29	5,58
26	100	45,43	25,54	11,42	10,35	6,45	5,38	4,49
27	100	52,31	41,77	25,01	24,11	18,84	6,19	2,03
28	100	85,45	73,54	72,43	70,27	66,58	65,74	61,5
29	100	69,94	56,99	43,9	33,04	18,01	6,99	2,7
30	100	68,84	32,83	33,39	18,7	15,65	3,19	0
31	100	77,99	51,2	30,94	24,08	17,38	12,44	8,9
33	100	76,26	51,82	43,02	27,79	19,83	13,13	8,9
34	100	80,37	64,41	46,33	31,21	12,01	10,88	9,8
35	100	73,83	37,92	29,51	15,62	15,22	3,07	0
36	100	76,19	55,03	37,96	31,88	16,67	12,7	9,68
37	100	93,68	84,39	73,73	70,23	65,48	61,83	54,43
35	100	61,28	43,87	23,26	16,3	11	6,69	4,07
38	100	64,4	46,36	30,11	26,52	3,58	1,67	0
40	100	68,91	57,97	33,91	26,41	15,94	4,84	1,47
41	100	90,72	80,8	76,82	65,32	61,05	57,66	54,46
43	100	73,84	51,02	42,41	35,31	23,79	11,09	5,77
46	100	57,93	41,15	25,4	19,66	12,53	5,29	2,23
47	100	64,06	55,2	40,44	29,78	10,4	0,64	0

Study Area:	Year:	Drug:
MAE SOT	2010	PV-EURY-3-ART

Drug conc.	SMI%
3,0	32,73
10,0	52,66
30,0	65,70
100,0	73,19
300,0	81,45
1000,0	87,99
3000,0	90,74

n =	31	S =	49,8116	f_s =	5,3366
a =	4,4210	A =	11,3852	f_{EC-50} =	2,3858
b =	0,2545	K =	7	f_{EC-90} =	10,4249
r =	0,9871	N' =	155	f_{EC-95} =	18,1136
χ^2 =	0,9485	R =	1000	f_{EC-99} =	56,2722

EC	Mean	95% Confidence Intervals Lower	Higher
EC_1	0,0010	0,0000	0,0586
EC_{16}	0,1954	0,0819	0,4662
EC_{50}	9,7330	4,0795	23,2214
EC_{84}	484,8164	203,2054	1156,6963
EC_{90}	1498,2211	143,7150	15618,8738
EC_{95}	6246,3502	344,8432	113143,8500
EC_{99}	90904,1172	1615,4359	5115373,7265

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VARIANCE ANALYSIS OF RESULTING DATA

The term is the probability that the difference is merely due to chance [60].

$$t = \frac{x1-x2}{\sqrt{(v1+v2)* {}^{1}/_{\eta}}}$$

x1 and x2 denoting the difference of the incidences, 2n the double of cases incorporated in the analysis, and v1 as well as v2 the vatiances between the two sets of figures [60].

Analysis

EURY1 – ART at IC_{50}

Result: 91,9466 Degrees of Freedom 54 (= 2,6908 at p = 0,01) significant synergism

EURY2 – ART at IC_{50}

Result: 37,2177 Degrees of Freedom 56 (= 2,6952 at p = 0,01) significant synergism

EURY3 – ART at IC_{50}

Result: 93,2021 Degrees of Freedom 52 (= 2,6864 at p = 0,01) significant synergism

EURY1 – ART at IC_{90}

Result: 32,1322 Degrees of Freedom 52 (= 2,6864 at p = 0,1) significant Synergism

EURY2 – ART at IC_{90}

Result: 41,3496 Degrees of Freedom 56 (= 2,6952 at p = 0,1) significant synergism

EURY3 – ART at IC_{90}

Result: 29,7526 Degrees of Freedom 52 (= 2,6864 at p = 0,1) significant Synergism

MAE SOT STUDIES 2010

Plasmodium vivax PATIENT RECORD FORM

Date	Pat. No.	Pat. Reg. MC	Sex	Age	Occupat.	Residence Country	Origin of Infection Country	No. Days Sympt. Before Seek. Treatm.	Comments
28.06.2010	1	14	m	30	forestry worker	Thailand	Myanmar	3d. fever	
30.06.2010	2	102	m	32	forestry worker	Thailand	Myanmar	7d. fever	
	3	23	m	24	forestry worker	Thailand	Myanmar	2d. fever	
01.07.2010	4	107	w	34	farmer	Myanmar	Myanmar	4d. fever	
	5	108	m	22	forestry worker	Myanmar	Myanmar	2d. fever	
	6	52	m	35	monk	Thailand	Thailand	4d. fever	
02.07.2010	7	114	m	18	worker	Thailand	Myanmar	11d. fever	
	8	121	m	79	farmer	Myanmar	Myanmar	9d. fever	
	9	64	m	35	forestry worker	Thailand	Myanmar	7d. fever	
	10	66	m	32	teacher	Thailand	Thailand	3d. fever	

05.07.2010	11	137	f	31	farmer	Myanmar	Myanmar	3d. fever	
	12	154	m	18	worker	Thailand	Thailand	4d. fever	
	13	161	f	44	worker	Myanmar	Myanmar	4d. fever	
06.07.2010	14	169	f	36	farmer	Myanmar	Myanmar	5d. fever	40,3°C
	15	172	f	10	student	Myanmar	Myanmar	3d. fever	
07.07.2010	16	176	f	14	student	Thailand	Myanmar	10d. fever	
08.07.2010	17	36	m	65	farmer	Thailand	Myanmar	8d. fever	
	18	186	m	13	student	Myanmar	Myanmar	3d. fever	
	19	197	m	25	forestry worker	Myanmar	Myanmar	3d. fever	
09.07.2010	20	211	m	78	monk	Myanmar	Myanmar	3d. fever	
12.07.2010	21	214	f	26	housewife	Thailand	Myanmar	7d. fever	
	22	215	f	21	worker	Thailand	Myanmar	3d. fever	
	23	216	m	24	worker	Thailand	Myanmar	20d. fever	
	24	109	f	38	worker	Thailand	Thailand	4d. fever	
	25	223	f	15	farmer	Myanmar	Myanmar	3d. fever	
	26	42	m	34	farmer	Thailand	Thailand	3d. fever	
	27	229	f	26	worker	Thailand	Myanmar	3d.	

								fever	
13.07.2010	28	46	m	17	student	Thailand	Thailand	4d. fever	venously blood
	29	238	f	24	farmer	Thailand	Thailand	3d. fever	venously blood
	30	239	m	15	student	Thailand	Thailand	4d. fever	venously blood
	31	119	m	16	worker	Thailand	Thailand	1d. fever	
14.07.2010	32	122	f	66	housewife	Thailand	Thailand	6d. fever	
15.07.2010	33	54	m	30	farmer	Thailand	Myanmar	3d. fever	
	34	266	m	16	farmer	Thailand	Thailand	4d. fever	
	35	270	m	24	worker	Thailand	Myanmar	3d. fever	
	36	136	m	29	forestry worker	Thailand	Thailand	3d. fever	F medium
19.07.2010	37	279	f	13	student	Myanmar	Myanmar	7d. fever	
21.07.2010	38	5	m	15	student	Thailand	Thailand	3d. fever	
	39	9	f	30	worker	Myanmar	Myanmar	1d. fever	venously blood
	40	11	m	39	laboratory	Myanmar	Myanmar	3d. fever	
22.07.2010	41	13	m	21	worker	Myanmar	Myanmar	4d. fever	
	42	16	m	35	worker	Myanmar	Myanmar	2d. fever	
23.07.2010	43	20	m	19	worker	Myanmar	Myanmar	3d. fever	

28.07.2010	44	26	m	56	soldier	Thailand	Thailand	4d. fever	
	45	50	m	13	student	Thailand	Myanmar	1d. fever	
	46	43	m	45	worker	Thailand	Thailand	2d. fever	
02.08.2010	47	82	m	24	farmer	Thailand	Thailand	3d. fever	venously blood

6. 5 List of abbrevations

a	intercept of regression
A	intermediate term for fS
A.	Anopheles
b	slope of regression
EC	Effective concentration
fS	factor of S
fEC	multiplication or division factor for obtainin 95 % confidential intervals of EC
K	number of drug concentration
n	number of isolate
N	number of points from EC 16 to EC 84
nM	Nanomolar
P.	Plasmodium
Pat. No.	Patient number
r	correlation of regression
R	factor of the highest compared to the lowest concentration tested
S	slope function
WHO	World Health Organization
χ^2	heterogeneity

6. 6 Curriculum vitae

Name:	**Taschauer Daniela**
Geburtsdatum:	**16.04.1985**
Schul- und Berufsausbildung:	
	Wintersemester 1991 – Sommersemester 1995 Volkschule: Loipersdorf (Burgenland)
	Wintersemester 1995 – Sommersemester 1999 Hauptschule: Markt-Allhau (Burgenland)
	Wintersemester 1999 – Sommersemester 2004 Höhere Bundeslehranstalt für wirtschaftliche Berufe: Oberwart (Burgenland)
	Wintersemester 2004 – Sommersemester 2005 Medizinstudium Medizinische Universität Wien
	Seit Wintersemester 2005 Lehramtstudium Psychologie & Philosophie und Biologie & Umweltkunde; Universität Wien
Sprachkenntnisse:	
Muttersprache:	Deutsch
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