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The active components and the pharmacological multi-target principle of STW 5 (Iberogast®)

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Abstract

The therapeutic equivalence of the multi-herbal drug combination STW 5 (Iberogast ®) with two synthetic standard drugs can be explained by an additive or overadditive pharmacological synergism. A review of the different chemical constituents contained in this fixed combination of nine herbal drug extracts and their dominant mechanisms of action shows that they correlate very well with the clinically relevant overall pharmacological profile of the multi-herbal drug combination. This comprises modulatory effects on gastro-intestinal motility, anti-inflammatory action, inhibitory effects on gastric acid production and anti-oxidative and radical-inhibiting properties. As a multi-drug preparation with a multitude of therapeutic targets relevant in functional gastrointestinal diseases, its pharmacological profile of action in accordance with the multi-target principle.

Keywords: Pharmacologically active constituents of STW 5 (Iberogast®); Relevance for therapy of functional dyspepsia (FD) and irritable bowel syndrome (IBS); Multi-drug- and target principles

Introduction

A herbal medicinal preparation derived from several herbal plant extracts contains a large number of secondary phytochemical compounds, which is considerably higher than that of an extract derived from a single drug. Such a combination of many constituents was therefore to be expected for STW 5 (Iberogast®) containing extracts from nine herbal drugs (Fig. 1).

As in earlier times only those compounds present in higher concentrations in a drug could be identified, research focussed on these main constituents with regard to chemical standardisation and pharmacological testing, even if it was not sure whether they included the main therapeutically relevant active ingredients of the extract. So they often could be only described as marker substances. Nowadays, it is known from numerous preclinical and clinical studies carried out with plant extracts that an entire extract in most cases has a better efficacy than one single main constituent isolated from such an extract. So it can be concluded, that in the pharmacological overall effects and the therapeutic efficacy of multi-extract preparations also numerous other constituents must be involved synergistically. Experimental studies with different combinations of active ingredients have demonstrated that such synergistic effects can be additive or superadditive (Wagner, 2006). The assumption that a superadditive effect is involved in the case of STW 5 is supported by the fact that the multi-extract preparation showed therapeutic

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Fig. 1. The herbal components of STW 5 (Iberogast®) are (left column) greater celandine (*Chelidonium majus* L.), peppermint (*Mentha piperita* L.), caraway (*Carum carvi* L.), (middle column) liquorice (*Glycyrrhiza glabra* L.), bitter candytuft (*Iberis amara* L.), chamomile (*Matricaria recutita* L.), (left column) milk thistle (*Silybum marianum* L.), lemon balm (*Melissa officinalis*), angelica (*Angelica archangelica* L.).

equivalence in comparative studies with two synthetic standard preparations (Nicolay, 1984; Rösch et al., 2002, 2006).

This result can only be explained when several active components of the preparation are acting synergistically and contributing to the overall effect and if it can be assumed that these individual components act on different pharmacological targets (Wink, 2005). At present, it is in detail not understandable how these synergistic effects arise in detail. Therefore, it is also not possible to theoretically predict the expected overall effect of a herbal drug or combination of drugs based on the known effects of distinct substances in the entire preparation. Also the rule applies that the effect of the entire preparation is greater than the sum of the effects of each single distinct substances. Future research on the reasons for such synergistic effects will at first have to elucidate what pharmacological and therapeutic contributions each distinct active component of an extract preparation provides and, secondly, which chemical substances or substance groups from the extracts are responsible for which specific pharmacological effects. This means to relate the pharmacological profile of an extract or a combination of extracts to the multi-causality of a disease state, which is a confirmation of the multi-target principle at the same time. When these

Table 1. Main substance classes and approximative number of secondary phytochemical compounds known from the drugs in STW 5 (sorted according to the number of compounds per class)

Substance group	*Iberis amara* totalis	Angelica root	Chamomile flower	Caraway fruit	Milk thistle fruit	Lemon balm leaves	Peppermint leaves	Celandine herb	Liquorice root	STW 5
Flavonoids	7[a]	1	36	9	20	4	12		17	106
Monoterpenes		11	5	8[e]		9	20[h]			53
Phenol carboxylic acids, depsides			5	15		12[g]	4	12		48
Phenylpropanoids				15					4	19
Alkaloids (as salts of chelidonic acid)								15		15
Furanocoumarins		13		2						15
Coumarins		4[c]	4	1					4	13
Triterpenes						7	4		2	13
Plant acids		7						3[i]		10
Sesquiterpenes		4	14[d]	1		3	1			9
Sterols, steroids					4		1		2	7
Saturated fatty acids				6						6
Dihydrofuranocoumarins		5								5
Volatile oil (drug specific)			1[d]	1[e]		1	1[h]		1	5
Biogenic amines, amino acids					2[f]			2		4
Cucurbitacins	4[b]									4
Macrocyclic lactones		4								4
Glucosinolates	3									3
Saponines									2[j]	2
Spiro ether			2							2
Alkanes							1			1
Dihydroxycoumarins			1							1
Lectins	1									1
Sinapic acid esters	1									1
Sum	16	53	57	69	29	36	44	32	32	368

Characteristic compounds from the individual drugs: [a]Kaempferol-3,4′-*O*-diglucosyl-7-*O*-rhamnoside; [b]Cucurbitacines E and I; [c]Osthole; [d]Bisabolol oxide A; [e]Carvone; [f]*N*-Malonyltryptophan; [g]Rosmarinic acid; [h]Menthol; [i]Chelidonic acid; [j]Glcyrrhizinic acid.

Table 2. Substance groups in STW 5 with motility modulating effects

Substance group	*Iberis amara* totalis	Angelica root	Chamomile flower	Caraway fruit	Milk thistle fruit	Lemon balm leaves	Peppermint leaves	Celandine herb	Liquorice root	STW 5	References
Monoterpenes		3		1	1	4	4			13	Brandt (1988), Reiter and Brandt (1985), Sadraei et al. (2001), Sousa et al. (1997), Taylor (1985), Wagner and Sprinkmeyer (1973)
Alkaloids (as salts of chelidonic acid)	2							10		12	Hanzlik (1920), Hiller et al. (1998), Kelentey (1960), Lin and Chang (1995), Ulrichova et al. (1983), Wrocinski (1963)
Flavonoids	2		2	1			4			9	Achterrath-Tuckermann et al., (1980), Ammon and Kaul (1992), Carle (2004), Hammad and Abdalla (1997), Lallement-Guilbert and Bezanger-Beauquesne (1970), Meckes et al. (2002), Revuelta et al. (2000), Trute et al. (1997)
Sesquiterpenes		1	4	1	1		1			8	Achterrath-Tuckermann et al., 1980, Ammon and Kaul (1992), Carle (2004), Mata et al. (1997)
Phenyl carboxylic acids		2		2		2		1		7	Hahn and Nahrstedt (1991, 1993), Trute et al. (1997), Xu et al. (1992)
Volatile oil (drug specific)			1	1		1	1		1	5	Brandt (1988), Debelmas and Rochat (1967), Reiter and Brandt (1985), Wagner and Sprinkmeyer (1973)
Phenylpropanoids		2	1							3	Ammon and Kaul (1992), Härmälä et al. (1991), Ko et al. (1992), Teng et al. (1994)
Coumarins		1	1							2	Härmälä et al. (1991), Ko et al. (1992), Teng et al. (1994), Patnaik et al. (1987)
Furanocoumarins		1								1	Patnaik et al. (1987)
Saponines									1	1	Schöpke (2004)
Spiro ether			1							1	Schöpke (2004)
	4	10	10	6	2	7	10	11	2	62	

Given is the number of substances with spasmolytic and antispasmodic effects. Investigations were conducted in vitro, in almost all cases in isolated ileum. Papaverine was mostly employed as reference. An electrical or pharmacological precontraction was induced in some studies.

Table 3. Substance groups in STW 5 with anti-inflammatory or antiphlogistic effects

Substance group	*Iberis amara* totalis	Angelica root	Chamomile flower	Caraway fruit	Milk thistle fruit	Lemon balm leaves	Peppermint leaves	Celandine herb	Liquorice root	STW 5	References
Flavonoids	5		4		7		1		5	22	Ammon and Kaul (1992), Blaschek et al. (2004), Carle (2004), Cechinel-Filho et al. (2000), Dehmlow et al. (1996), Della Loggia (1985), De La Puerta et al. (1996), Ferrandiz et al. (1990), Fuchs and Milbrandt (1993), Gupta et al. (1971), Hänsel et al. (1999), Lambev et al. (1980), Lin et al. (2000), Nagumo et al. (1999), Varga et al. (2001)
Phenyl carboxylic acids		2	2	6		3				13	Chen et al. (1995), Englberger et al. (1988), Fernandez et al. (1998), Giovannini et al. (2002), Hirabayashi et al. (1995), Kimura et al. (1987), Langner et al. (1987), Lim et al. (2002), Nguyen and Lee (1992), Hart et al. (2000), Krakauer (2002), Peake et al. (1991), Rampart et al. (1986), Rossi et al. (2002), Sahu et al. (1999), Sakai et al. (1997, 1999)
Sesquiterpenes		1	8	1		1	1			12	Aggag and Yousef (1972), Ammon and Kaul (1992), Ammon and Sabieraj (1996), Carle (2004), Deininger (1956), Jakovlev et al. (1979, 1983), Jakovlev and Schlichtegroll (1969), Lenfeld et al. (1986), Martin et al. (1993), Tambe et al. (1996), Zapf et al. (1996)
Dihydrofuranocoumarins		7								7	Abad et al. (2001), Adjangba et al. (1975), Chen et al. (1995), Garcia-Argaez et al. (2000), Murakami et al. (1999), Roos et al. (1997)
Coumarins		3	1	1					1	6	Chen et al. (1995), Hardt and Ritschel (1983), Liu et al. (1998), Resch et al. (1998), Roos et al. (1997), Silvan et al. (1996)

Alkaloids (as salts of chelidonic acid)								5		5	Lenfeld and Kroutil (1981), Saeed et al. (1997), Tanaka et al. (1993)
Monoterpenes		2	1	1		1				5	Hart et al. (2000), Lim et al. (2002), Martin et al. (1993), Peana et al. (2002)
Cucurbitacins	4									4	Jayaprakasam et al. (2003), Miro (1995), Peters et al. (1997)
Saponines									2	2	Capasso et al. (1983), Kroes et al. (1997), Nagumo et al. (1999), Ohuchi et al. (1981), Safayhi and Sauer (1997), Yasukawa et al. (1988, 1991)
Saturated fatty acids				2						2	Biesalski (1999)
Spiro ether			2							2	Ammon and Kaul (1992), Carle (2004), Della Loggia (1985), Fuchs and Milbrandt (1993)
Triterpenes						2				2	Baricevic et al. (2001), Liu (1995), Ringbom et al. (1998), Simon et al. (1992), Singh et al. (1992)
Alkanes							1			1	Carbajal et al. (1998)
Dihydroxycoumarins			1							1	Neichi et al. (1983), Panossian (1984), Sekiya et al. (1982), Tubaro et al. (1988)
Volatile oil (drug specific)			1							1	Wagner et al. (1986)
	9	15	20	11	7	7	3	5	8	85	

Effects were documented both in vitro and in the majority of cases in vivo as well, using accepted models including LPS-stimulated macrophages and determination of the activity of 5-LOX or 12-LOX and COX. The in vitro models included rat paw oedema test, TPA-induced mouse ear oedema, croton ear oedema test and UV erythema test.
Given is the number of substances with anti-inflammatory effects.

Table 4. Substance groups in STW 5 with anti-oxidative or radical inhibiting effects

Substance group	*Iberis amara* totalis	Angelica root	Chamomile flower	Caraway fruit	Milk thistle fruit	Lemon balm leaves	Peppermint leaves	Celandine herb	Liquorice root	STW 5	References
Flavonoids	1		2	3	8	1	2		6	23	Areias et al. (2001), Aviram and Fuhrman (1998), Bosisio et al. (1992), Choi et al. (2000), Fuhrman et al. (1997), Fuchs and Milbrandt (1993), Glasser et al. (2002), Kahkonen and Heinonen (2003), Lamaison et al. (1988, 1991), Lim et al. (2002), Manez et al. (1999), Ratty et al. (1988), Romanova et al. (2001), Schöpke (2004), Stahl-Biskup (2004), Valenzuola et al. (1989)
Phenyl carboxylic acids		2	3	7		3				15	Andreasen et al. (2001), Bourne and Rice-Evans (1997), Fabre et al. (2000), Heilmann et al. (2000), Hirota et al. (2000), Jung et al. (1999), Kong et al. (2001), Kono et al. (1997, 1998), Kuo et al. (2002), Lamaison et al. (1988, 1991), Lim et al. (2002), Masaki et al. (1995), Medina et al. (2002), Nardini et al. (1997), Ogiwara et al. (2002), Raneva et al. (2001), Scott et al. (1993), Tsuchiya et al. (1996), Tsuchiya et al. (1998), Uchida et al. (1996), Yamanaka et al. (1997), Yeh and Yen (2003)
Coumarins		1		1		1			1	4	Baccard et al. (2000), Chang and Chiang (1995), Lin et al. (2000), Martin-Aragon et al. (1998), Pillai et al. (1999), Schöpke (2004), Toda 2002
Monoterpenes			3	1						4	Choi et al. (2000), Dapkevicius et al. (2002), Vardar-Unlu et al. (2003)
Volatile oil (drug specific)				1					1	2	Choi et al. (2000), Farag and el Khawas (1998)
Triterpenes						2				2	Balanehru and Nagarajan (1991), Han et al. (1989), Han et al. (1997), Heo et al. (2002), Lee et al. (2002)
Alkanes							1			1	Ramanarayan et al. (2000)
Saponines									1	1	Schöpke (2004)
Sinapic acid esters	1									1	Fabre et al. (2000)
	2	3	8	13	8	7	3		9	53	

Given is the number of substances, for which effects in established experimental models have been shown, such as lipid (per-)oxidation, inhibition of DPPH radicals and inhibition of LDL oxidation.

different single effects of the preparation are known, this has to be standardised in order to ensure reproducible pharmacological and therapeutic results. Concerning the combination product STW 5 the different extracts contained in the combination must be standardised in terms of their pharmacologically relevant components and properties. This strategy has been employed in the pharmacological research on STW 5 and on the extracts contained.

As a result of these investigations, a total of five predominating pharmacological actions were determined, as is shown in the following single contributions in this supplementary volume. All these actions show a direct therapeutic relationship to the symptoms of functional gastro-intestinal diseases.

They include

- a tonicising, prokinetic action,
- a gastro-intestinal spasmolytic action,
- an anti-secretory action,
- an anti-inflammatory action and
- an anti-oxidative as well as a radical-inhibiting action.

Extensive literature research was carried out (e.g. via MEDLINE and EMBASE) to list the known chemical constituents of the drugs from STW 5 (Table 1) and to relate them to three main pharmacological actions (Tables 2–4).

Constituents and substance classes from the herbal drugs in STW 5

All herbal drugs contained in STW 5 have been very well investigated analytically. So, as was to be expected, a large number of secondary chemical constituents could be identified for each of the nine drugs. A total of more than 350 distinct chemical compounds, including about 200 with known pharmacological activity, were found and classified into substance classes. Table 1 lists substance classes and numbers of chemical compounds, which have been identified for the different drugs, and mentions characteristic compounds.

The following five main substance classes dominate in the nine plant drugs based on the data found in the literature:

- terpenes (including sesquiterpenes, monoterpenes; in almost all drugs),
- volatile oil (in almost all drugs),
- coumarins (in some of the drugs),
- flavonoids with almost all subclasses (in all drugs) and
- phenol carboxylic acids (in almost all drugs).

Substance groups, which have been linked to adverse effects at very high doses, were only mentioned for one or two drugs, each. These are the alkaloids (in *Chelidonium majus*), dihydrofuranocoumarins (in *Angelica archangelica*) and the sesquiterpene lactones (in *Angelica archangelica* and *Matricaria recutita*). So these substance groups combine in a subadditive way in terms of possible combined effects within the combination.

Prolonged application of high doses of *Chelidonium* extracts has been linked to some rare cases of reversible hepatotoxic reactions, which have been attributed to the alkaloid content of the drug. As most of these cases were reported from patients with pre-existing biliary complaints, causality is under discussion (Nahrstedt and Weber, 2005). In doses of *Chelidonium* alkaloids as low as those applied with STW 5, or even more than 10-fold higher, no such cases have ever been reported. Toxicological data do not point to any remarkable toxicity or specific hepatotoxic potential after acute or prolonged oral application of *Chelidonium* alkaloids (Becci et al., 1987; Kosina et al., 2003) in doses several orders of magnitude higher than those applied in therapy with STW 5.

Angelicae radix contains furanocoumarins, mainly xanthotoxol, for which phototoxicity has been reported after application of high doses of about 1 mg/kg b.w. and intensive UV A irradiation (Teuscher and Lindequist, 1994). These doses are more than three orders of magnitude above doses, which can be achieved by therapeutic doses of STW 5. This is in accordance with animal studies showing LD_{50} values several orders of magnitude above those used with STW 5 in acute testing in rats and mice (Sethi et al., 1992) as well as chronic testing in rats over 6 month (Teuscher and Lindequist, 1994). Moreover sesquiterpenlactone levels are very far below toxicological relevance in doses of *Angelica* as well as *Matricaria* extracts applied with STW 5, so relevant additive effects are unlikely.

Additive effects therefore are not to be expected in substance classes with possible toxicological relevance, and indeed STW 5 has a very favourable safety profile (Rösch et al., 2006). For the pharmacologically relevant other substance classes, which generally show a broad spectrum of action, supraadditive effects can be assumed.

Pharmacological actions of phytochemical compounds from the drugs contained in STW 5

The structured evaluation of the pharmacological literature yielded numerous information concerning the

effects of the individual substances. The following main pharmacological effects were found:

- Motility modulating effects (Table 2).
- Anti-inflammatory effects (Table 3).
- Anti-oxidative and radical-inhibiting effects (Table 4).

These effects are dealt with in detail in the following. Only those substances are included in the Tables 2–4, for which published data on the appropriate actions are available.

Modulating effects on gastro-intestinal motility

Motility modulating effects have been reported from in vitro studies from a total of at least 7 substance classes. Spasmolytic and antispasmodic effects are subsumed under this topic.

Volatile oil (as drug-specific oils, for 5 drugs), sesquiterpenes with subclasses (for 5 drugs), coumarins (for 2 drugs), flavonoids with subclasses (for 3 drugs), monoterpenes (for 5 drugs) and phenol carboxylic acids (for 4 drugs) can be given as predominating substance classes from STW 5 known to have effects on gastro-intestinal motility. The substance classes of the alkaloids and the bisabols (as subclass of the sesquiterpenes), were found for only one drug each, and other substance classes were only mentioned in isolated cases.

The spasmolytic effects were investigated in isolated ileum in almost all studies, using papaverine as reference substance in most cases. In some studies, an electrical or chemical pre-contraction was induced in order to thus elucidate the antispasmodic properties.

Motility modulating effects have been shown pharmacologically for the combination STW 5 as dual mechanism of action in the intestine, relaxing in spastic intestine (Hagelauer et al., 2005; Heinle et al., 2006; Yuece et al., 2006; Michael et al., 2006) and tonicising in atonic intestine (Okpanyi et al., 1993; Ammon et al., 2006), and as region specific effects, relaxing gastric corpus and fundus and tonicising the antrum (Schemann et al., 2006). This region specific effect in stomach has also been confirmed in vivo by clinical pharmacological data (Pilichiewicz et al., 2006). In therapy, they are involved in its action regarding functional gastro-intestinal diseases, as these are characterised predominantly by motility disorders (Allescher, 2006). The literature data on the spasmolytic and antispasmodic effects of the phytochemical compounds contained in STW 5 can be related to its mechanisms of action. A motility modulating effect of STW 5 is thus plausible from the pharmacological properties of the contained substances.

Anti-inflammatory effects

Anti-inflammatory or antiphlogistic properties have been reported from in vitro and in vivo studies from a total of at least 7 substance classes.

Flavonoids with subclasses (for 5 drugs), sesquiterpenes with subclasses (for 5 drugs), coumarins (for 4 drugs), monoterpenes (for 4 drugs) and phenol carboxylic acids (for 4 drugs) have to be mentioned as the predominating substance classes in several drugs. In addition, there are alkaloids and cucurbitacines for 1 drug in each case. Other substance classes are to be mentioned in isolated cases.

The anti-inflammatory effects were examined and demonstrated in vitro as well as in vivo (in the majority of cases) in the studies, using scientifically accepted methods. The in vitro methods used included among others the measurement of liberated inflammation mediators by lipopolysaccharide (LPS)-stimulated macrophages and the activities of 5-lipoxygenase (5-LOX) or 12-LOX and cyclooxygenase (COX). The rat paw oedema test, the 12-*o*-tetradecanoylphorbol-13-acetate (TPA)-induced mouse ear oedema, the croton ear oedema test and the UV erythema test were used among others in vivo.

The anti-inflammatory effects shown for the combination STW 5 (Khayyal et al., 2001, 2006; Germann et al., 2006; Michael et al., 2006) can thus be convincingly related to the activities of the single substances contained in this combination and to their reported anti-inflammatory or antiphlogistic effects and are thus plausible also from the activities of these substances.

Anti-oxidative and radical inhibiting effects

Anti-oxidative or radical inhibiting effects were reported from experimental in vitro studies for a total of about 7 substance classes. These effects are of possible relevance to anti-ulcerative, ulcer-protective and anti-inflammatory effects.

As expected, the flavonoids with subclasses (for 7 drugs) and the phenol carboxylic acids (for 4 drugs) are the predominating substance classes in several drugs. Furthermore, monoterpenes (for 2 drugs), coumarins (for 4 drugs) and volatile oil (for 2 drugs) are listed in addition to other individual representatives.

Accepted and reproducibly described models were used in the experimental studies, such as the lipid (per)oxidation, the inhibition of 1,1-diphenyl-2-picryl-hydracyl (DPPH) radicals and the inhibition of low-density lipoprotein (LDL) oxidation.

A contribution of the antioxidative actions reported for the components to the effect of STW 5 appears plausible in particular due to the involvement of radical

related processes in inflammation. The antiinflammatory action shown for STW 5 (Schempp et al., 2006, Germann et al., 2006) is in accordance with these data (Saller et al., 2002).

Summary and conclusion

STW 5 (Iberogast®) is a combination of nine herbal drugs containing many different phytochemical substances. The properties of similarly acting substance groups complement each other and contribute all to varying degrees to the overall pharmacological activity profile of the combination.

The superior adaptation of the profile of action of the combination to its therapeutic indication is the supposed cause for the advantages in comparison to a mono preparation. While a single extract can be optimized to give the desired therapeutic effect only to a limited degree, e.g. by means of plant cultivation or pharmaceutical modifications (as the choice of the extraction medium), a combination of several extracts can be specifically modified to provide an optimized efficacy and safety profile for a certain indication. As it is shown by the analysis of the pharmacological data on the substance classes contained in STW 5, there are nevertheless no principial but only gradual pharmacological differences between a single drug and a combination of several different drugs. As might be seen in the pharmacological profile of action of STW 5, more combination partners can provide a better adaption of the action profile for an indication. This can be a decisive therapeutic advantage particularly for certain complex, multifactorial disease syndromes such as those of functional gastro-intestinal diseases.

Reviews or monographs such as those of the former Commission E of the Federal German Health Ministry are of use in characterizing the safety of the drugs, however, they often provide only very limited assistance in an attempt to characterize the pharmacological overall effects of combinations. It is therefore of primary importance to elucidate the pharmacological and toxicological properties of the combination in the first place. This has been carried out for STW 5 in a comprehensive manner 2006).

As already mentioned above, the following effects have been demonstrated for STW 5 up to now using accepted standard models of pharmacological research:

- gastro-intestinal spasmolytic action,
- tonicising prokinetic action,
- inhibition of gastric acid production,
- antiulcerogenic effects as well as
- anti-inflammatory or antiphlogistic effects.

The summarized listing of the single substances to be expected or found in STW 5 and the effects described for them results in an overall picture of a medicine active in irritable stomach and irritable bowel syndrome. Of the effects known for the phytochemical components of STW 5, those effects were most often mentioned which are logically related to the above-mentioned motility modulating, anti-inflammatory, anti-oxidative and radical inhibiting effects of STW 5.

The combination of the nine drugs in STW 5 (Iberogast®) can therefore be regarded as reasonable from a pharmacological perspective, targeting a multitude of mechanisms relevant in the therapy of functional dyspepsia and irritable bowel syndrome according to the multi-target principle.

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