SCIENTIFIC SECTION

THE STRYCHNINE-BRUCINE RATIO OF NUX VOMICA AND THE RELATIVE POTENCY OF THESE ALKALOIDS.

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RESULTS AND OBSERVATIONS.

A.—CHEMICAL.

The tables which follow are arranged so that the results obtained with each sample of crude drug are grouped with those obtained with the fluidextract and the tincture manufactured from that particular powdered sample of Nux Vomica.

Three assays were carried out on each sample, and on the tincture and the fluidextract made therefrom. The weight of total alkaloids was determined first, the brucine then destroyed by oxidation, and the weight of brucine calculated by subtracting the weight of the residue (the strychnine) from that of the total alkaloids.

The percentages found in the tincture tables have been expressed in terms of amounts representing equivalent quantities to the powdered drug and fluidextract. This was done in order that the values might be compared more readily.

TABLE I.—SAMPLE NO. 1 POWDERED NUX VOMICA, FLUIDEXTRACT, TINCTURE.

Assay of	Gm. or Cc. Sample.	Gm. Total Alk.	Gm. Strych.	Gm. Bruc.	% Tot. Alk.	% Strych.	% Bruc.	Ratio S–B.
Drug	9.8064	0.2160	0.0922	0.1238	2.200	0.939	1.261	43–57
Drug	10.0519	0.2180	0.0950	0.1230	2.170	0.940	1.230	43–57
Drug	9.5503	0.2100	0.0894	0.1206	2.190	0.932	1.258	43–57
Fldext.	10	0.2311	0.0970	0.1341	2.311	0.970	1.391	42–58
Fldext.	10	0.2264	0.0971	0.1293	2.264	0.971	1.293	43–57
Fldext.	10	0.2283	0.0989	0.1294	2.283	0.989	1.294	43–57
Tr.	50	0.1118	0.0465	0.0653	2.230	0.926	1.304	42–58
Tr.	50	0.1139	0.0486	0.0653	2.271	0.968	1.303	43–57
Tr.	50	0.1119	0.0466	0.0653	2.230	0.928	1.302	42–58

The average ratio of strychnine to brucine in this crude drug and its galenical preparations was practically uniform, *viz.*, 43 parts of strychnine to 57 parts of brucine.

This sample of drug was not labeled U. S. P., and the results of the assays indicate that it is not up to official standards.

TABLE II.—SAMPLE NO. 2 POWDERED NUX VOMICA, FLUIDEXTRACT, TINCTURE.

Assay of	Gm. or Cc. Sample.	Gm. Total Alk.	Gm. Strych.	Gm. Bruc.	% Tot. Alk.	% Strych.	% Bruc.	Ratio S–B.
Drug	10.5942	0.2228	0.0992	0.1236	2.103	0.936	1.167	45–55
Drug	11.3735	0.2440	0.1090	0.1390	2.150	0.960	1.190	45–55
Drug	10.8728	0.2356	0.1062	0.1250	2.161	0.975	1.186	45–55
Fldext.	10	0.2149	0.0963	0.1186	2.149	0.963	1.186	45–55
Fldext.	10	0.2125	0.0933	0.1193	2.125	0.933	1.193	44–56
Fldext.	10	0.2104	0.0948	0.1156	2.104	0.948	1.156	45–55
Tr.	50	0.1093	0.0490	0.0603	2.186	0.981	1.205	45–55
Tr.	50	0.1075	0.0496	0.0579	2.150	0.973	1.177	45–55
Tr.	50	0.1098	0.0492	0.0606	2.186	0.983	1.203	45–55

The strychnine-brucine ratio was essentially the same throughout, *viz.*, 45 of strychnine to 55 of brucine in the powdered drug, the fluidextract and the tincture.

This sample, too, is below pharmacopœial requirements for total alkaloidal content.

TABLE III.—SAMPLE NO. 3 POWDERED NUX VOMICA, FLUIDEXTRACT, TINCTURE.

Assay of	Gm. or Cc. Sample.	Gm. Total Alk.	Gm. Strych.	Gm. Bruc.	% Alk.	% Strych.	% Bruc.	Ratio S-B.
Drug	10.9335	0.2690	0.1222	0.1468	2.461	1.120	1.341	46–54
Drug	10.3523	0.2570	0.1164	0.1406	2.483	1.131	1.352	46–54
Drug	10.5528	0.2538	0.1158	0.1380	2.412	1.101	1.311	46–54
Fldext.	10	0.2380	0.1105	0.1275	2.380	1.105	1.275	46–54
Fldext.	10	0.2376	0.1088	0.1288	2.376	1.088	1.288	46–54
Fldext.	10	0.2349	0.1070	0.1279	2.349	1.070	1.279	46–54
Tr.	50	0.1263	0.0580	0.0683	2.526	1.159	1.367	46–54
Tr.	50	0.1252	0.0571	0.0681	2.504	1.142	1.362	46–54
Tr.	50	0.1249	0.0574	0.0675	2.498	1.154	1.344	45–55

The ratio of strychnine to brucine in the tincture, the fluidextract and the powdered drug was 46 to 54.

TABLE IV.—SAMPLE NO. 4 POWDERED NUX VOMICA, FLUIDEXTRACT, TINCTURE.

Assay of	Gm. or Cc. Sample.	Gm. Total Alk.	Gm. Strych.	Gm. Bruc.	% Tot. Alk.	% Strych.	% Bruc.	Ratio S-B.
Drug	11.7569	0.2814	0.1358	0.1456	2.394	1.124	1.270	47–53
Drug	11.2453	0.2720	0.1332	0.1389	2.419	1.140	1.280	47–53
Drug	10.3632	0.2438	0.1134	0.1304	2.353	1.102	1.251	47–53
Fldext.	10	0.2490	0.1181	0.1309	2.490	1.181	1.309	47–53
Fldext.	10	0.2424	0.1142	0.1282	2.424	1.142	1.282	47–53
Fldext.	10	0.2446	0.1134	0.1312	2.446	1.134	1.312	47–53
Tr.	50	0.1227	0.0583	0.0644	2.454	1.168	1.286	47–53
Tr.	50	0.1190	0.0571	0.0619	2.380	1.142	1.238	47–53
Tr.	50	0.1227	0.0584	0.0643	2.454	1.167	1.287	47–53

This sample of powdered Nux Vomica is slightly below official specifications for total alkaloidal content, but the preparations made from it come up to official requirements.

The strychnine-brucine ratio was found to be 47 to 53 in the powdered drug, the fluidextract and the tincture.

TABLE V.—SAMPLE NO. 5, POWDERED NUX VOMICA, FLUIDEXTRACT, TINCTURE.

Assay of	Gm. or Cc. Sample.	Gm. Total Alk.	Gm. Strych.	Gm. Bruc.	% Tot. Alk.	% Strych.	% Bruc.	Ratio S-B.
Drug	11.5633	0.2350	0.1144	0.1206	2.03	0.989	1.044	49–51
Drug	11.9918	0.2400	0.1164	0.1236	2.00	0.970	1.030	49–51
Drug	9.8784	0.1980	0.0972	0.1008	2.00	0.986	1.014	49–51
Fldext.	10	0.1976	0.0978	0.0998	1.976	0.978	0.998	49–51
Fldext.	10	0.1967	0.0959	0.1008	1.967	0.959	1.008	49–51
Fldext.	10	0.1961	0.0953	0.1008	1.961	0.953	1.008	49–51
Tr.	50	0.0992	0.0485	0.0507	1.984	0.916	1.068	49–51
Tr.	50	0.0967	0.0470	0.0497	1.934	0.934	1.095	49–51
Tr.	50	0.0991	0.0486	0.0505	1.982	0.969	1.013	49–51

The ratio of strychnine to brucine was constant for the powdered drug, the fluidextract and the tincture; *viz.*, 49 parts of strychnine to 51 parts of brucine.

This sample of crude drug, although bearing a label stating that it was in accord with the U. S. P. requirements for total alkaloids, assayed below the official requirements. The same was true of the fluidextract and tincture.

TABLE VI.—SAMPLE NO. 6, POWDERED NUX VOMICA, FLUIDEXTRACT, TINCTURE.

Assay of	Gm. or Cc. Sample.	Gm. Total Alk.	Gm. Strych.	Gm. Bruc.	% Tot. Alk.	% Strych.	% Bruc.	Ratio S-B.
Drug	11.6149	0.2756	0.1142	0.1614	2.373	0.985	1.338	41–59
Drug	11.6895	0.2758	0.1122	0.1636	2.371	0.965	1.406	41–59
Drug	10.6839	0.2534	0.1036	0.1498	2.372	0.968	1.404	41–59
Tr.	50	0.1210	0.0505	0.0705	2.420	1.001	1.419	41–59
Tr.	50	0.1210	0.0503	0.0707	2.420	1.006	1.414	41–59
Tr.	50	0.1203	0.0505	0.0698	2.406	1.010	1.396	41–59

The ratio of strychnine to brucine was constant in both the powder and the tincture, *viz.*, 41 parts of strychnine to 59 parts of brucine.

The powdered drug is a little below U. S. P. specifications, but the tincture assays within the pharmacopœial limits.

TABLE VII.—SAMPLE NO. 7, POWDERED NUX VOMICA AND TINCTURE.

Assay of	Gm. or Cc. Sample.	Gm. Total Alk.	Gm. Strych.	Gm. Bruc.	% Tot. Alk.	% Strych.	% Bruc.	Ratio S-B.
Drug	12.5081	0.2982	0.1280	0.1702	2.384	1.023	1.361	43–57
Drug	10.4704	0.2478	0.1080	0.1439	2.386	1.039	1.347	43–57
Drug	9.9832	0.2374	0.1045	0.1329	2.378	1.047	1.331	44–56
Tr.	50	0.1176	0.0496	0.0680	2.352	0.992	1.360	43–57
Tr.	50	0.1193	0.0520	0.0673	2.386	1.040	1.346	43–57
Tr.	50	0.1175	0.0511	0.0664	2.350	1.022	1.328	43–57

The ratio of strychnine to brucine was 43 *plus* strychnine to 57 *minus* brucine in both powder and tincture. Only a tincture was prepared.

This sample of powdered drug and its tincture are slightly below pharmacopœial requirements.

TABLE VIII.—SAMPLE NO. 8, POWDERED NUX VOMICA, TINCTURE.

Assay of	Gm. or Cc. Sample.	Gm. Total Alk.	Gm. Strych.	Gm. Bruc.	% Tot. Alk.	% Strych.	% Bruc.	Ratio S-B.
Drug	11.1093	0.2532	0.1360	0.1172	2.279	1.224	1.055	54–46
Drug	13.0740	0.2950	0.1598	0.1352	2.256	1.222	1.034	54–46
Drug	11.3560	0.2564	0.1384	0.1180	2.258	1.219	1.039	54–46
Tr.	50	0.1167	0.0652	0.0515	2.334	1.384	0.950	55–45
Tr.	50	0.1162	0.0621	0.0541	2.324	1.243	1.081	54–46
Tr.	50	0.1159	0.0623	0.0536	2.318	1.249	1.069	54–46

The ratio of strychnine to brucine in both powdered drug and tincture was 54 to 46.

Although this sample of crude drug bore a U. S. P. label, both the tincture and powdered drug are well below official requirements.

Seven of the eight samples assayed less strychnine than brucine, varying from a low strychnine ratio of 41 to 59 brucine, to a high ratio of 54 strychnine to 46 brucine. Only one sample assayed more strychnine than brucine, this ratio being 54 strychnine to 46 brucine.

B. PHARMACOLOGIC.

In order to obtain doses which would cause convulsions in approximately the same length of time, several series of preliminary observations on each specie of animal employed in the study were made.

TABLE IX.—FROGS—STRYCHNINE.

The frogs were injected with a solution of Strychnine Sulphate, using eight milligrams per kilogram-body-weight.

Frog No.	Wt. in Gm.	Minutes to Hypersensitivity.	Minutes to Convulsions.
1	18.1	6	9
2	23.6	4	7
3	18.4	4	10
4	18.2	4	6
5	21.3	4	6
Averages:		$4^{2}/_{5}$	$7^{3}/_{5}$

TABLE X.—FROGS—BRUCINE.

The frogs were injected with a solution of Brucine Sulphate, using eighty times the dose of Strychnine Sulphate or 640 milligrams per kilogram-body-weight.

Frog No.	Wt. in Gm.	Minutes to Hypersensitivity.	Minutes to Convulsions.
1	17.1	3	6
2	15.9	4	7
3	13.4	3	5
4	17.3	3	6
5	21.0	3	8
Averages:		$3^{1}/_{5}$	$6^{2}/_{5}$

The relative potency of strychnine and brucine in the frog is *one to eighty.*

TABLE XI.—RABBITS—STRYCHNINE.

The rabbits were injected subcutaneously in the abdominal region with a solution of Strychnine Sulphate, using 0.5 milligram per kilogram-body-weight.

Rabbit No.	Wt. in Kilograms.	Minutes to Hypersensitivity.	Minutes to Convulsions.
1	1.42	13	18
2	1.91	12	19
3	1.36	12	18
4	1.36	11	17
5	1.60	14	16
6	1.25	12	18
Averages:		$12^{1}/_{3}$	$17^{2}/_{3}$

TABLE XII.—RABBITS—BRUCINE.

The rabbits were injected subcutaneously as in Table III, with a solution of Brucine Sulphate, using thirty-seven times the dose of Strychnine Sulphate or 18.5 milligrams per kilogram-body-weight.

Rabbit No.	Wt. in Kilograms.	Minutes to Hypersensitivity.	Minutes to Convulsions.
1	1.42	13	19
2	1.30	12	18
3	1.53	12	16
4	1.54	12	16
5	0.91	10	15
6	1.96	12	16
Averages:		12	$16^{2}/_{3}$

The relative toxicity of strychnine to brucine in the rabbit, is therefore, *one to thirty-seven.*

TABLE XIII.—DOGS—STRYCHNINE.

The dogs were injected subcutaneously with a solution of Strychnine Sulphate, using 0.3 milligram per kilogram-body-weight.

Dog. No.	Wt. in Kilograms.	Minutes to Hypersensitivity.	Minutes to Convulsions.
1	3.80	12	13
2	9.00	9	10
3	2.60	10	13
4	5.00	10	14
5	7.03	11	15
Averages:		$10^{2}/_{5}$	13

TABLE XIV.—DOGS—BRUCINE.

The dogs were injected subcutaneously with a solution of Brucine Sulphate, using forty-five times the dose of Strychnine Sulphate or 13.5 milligram per kilogram-body-weight.

Dog No.	Wt. in Kilograms.	Minutes to Hypersensitivity.	Minutes to Convulsions.
1	4.40	10	11
2	3.75	10	12
3	9.60	11	14
4	7.00	9	14
5	8.00	10	12
Averages:		10	$12^{3}/_{5}$

The relative toxic ratio of strychnine to brucine in the dog is, therefore, *one to forty-five.*

TABLE XV.—CATS—STRYCHNINE.

The dose of Strychnine Sulphate given to the cats subcutaneously, in the abdominal region, was 0.4 milligram per kilogram-body-weight.

Cat No.	Wt. in Kilograms.	Minutes to Hypersensitivity.	Minutes to Convulsions.
1	2.70	18	19
2	1.93	11	16
3	1.37	16	..
4	2.40	9	17
5	1.14	10	12
Averages:		$12^{4}/_{5}$	$15^{4}/_{5}$

TABLE XVI.—CATS—BRUCINE.

The dose of Brucine Sulphate given to the cats subcutaneously, in the abdominal region, was thirty-five times the dose of Strychnine Sulphate, or 14 milligrams per kilogram-body-weight.

Cat No.	Wt. in Kilograms.	Minutes to Hypersensitivity.	Minutes to Convulsions.
1	1.70	8	12
2	2.27	10	15
3	3.30	10	15
4	1.60	10	17
5	1.80	10	14
Averages:		$9^{3}/_{5}$	$14^{3}/_{5}$

The relative toxic ratio of strychnine to brucine in the cat is *one to thirty-five.* The strychnine cats showed a greater degree of individual susceptibility than any of the animals observed.

The relative degree of toxicity of strychnine to brucine was found to be relatively constant with the warm-blooded animals employed. The cold-blooded animal, the frog, showed a much greater ratio.

Convulsions appeared in all the animals under observation. The interval of time to death is not recorded in the tables, but the animals to which strychnine was administered showed about a fifty per cent recovery, whereas, in those to which brucine had been given, death ultimately occurred in almost one hundred per cent.

CONCLUSIONS.

1. Contrary to the reports of many investigators, there is fair uniformity in the percentages of total alkaloids in Nux Vomica, the lowest found being 2.000, and the highest 2.483. The average is 2.272, which is below the U. S. P. requirement of 2.5 per cent.

2. The generally accepted statement that strychnine and brucine occur in practically equal amounts is not correct. This study showed the following ratios for the eight samples examined:

Strychnine.	Brucine.	Strychnine.	Brucine.
41	59	46	54
43	57	47	53
43	57	49	51
45	55	54	46

Six of the eight samples, all showing a higher brucine content, gave an average strychnine-brucine ratio of 44 to 56. But one sample came close to a 50–50 ratio; and but one showed a higher strychnine content.

3. The rather general statement in the literature that galenical preparations of Nux Vomica contain more strychnine than brucine, is contrary to the findings of this investigation.

4. The relative amounts of strychnine and brucine present in preparations of Nux Vomica were found to be in fair accord with the relative amounts present in the crude drug.

5. Specie susceptibility is a decided influencing factor in any study of the relative potency of strychnine and brucine, and this fact probably accounts for the variations in mathematical comparisons which have been reported.

6. The cat and rabbit show a fairly close strychnine-brucine-toxicity-ratio, *viz.*, 1 to 37 for the rabbits, and 1 to 35 for the cat. The ratio for the dog was 1 to 45, and for the frog, 1 to 80. The dog and the rabbit are the more satisfactory animals for this type of comparative study.

7. The statement that strychnine is many times more potent than brucine, has been confirmed by this investigation.

8. The general statement that death is usually produced in brucine poisoning without even a trace of spasm, is not in agreement with the findings of this investigation. All brucinized animals showed convulsions which were of a much more severe type than those produced by strychnine.

NOTE: This investigation is the first reported systematized study of the strychine-brucine ratio in powdered Nux Vomica, its tincture and its fluidextract, and of the relative toxicities of strychnine and brucine.

9. A more accurate and satisfactory method for standardizing Nux Vomica and its preparations, from a pharmacodynamic and therapeutic angle, would consist in determining both the amount of total alkaloids and the amount of Strychnine. However, since a one-determination method appears to be more practicable, the strychnine content is a more satisfactory standard than the present total alkaloid content.

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New Pharmacy regulations in Turkey require that part of the pharmacy must be devoted to dispensing; a special laboratory must be installed for preparation of galenicals; proper provisions must be made for storing drugs and preparations. Certain serums must be stocked; also distilled and sterilized water. All pharmacies must be inspected at least twice a year.