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META ANALYSIS OF 195 STUDIES FOR ASSESSING RENOPROTECTIVE ROLE OF PLANT SPECIES IN THE GENTAMICIN EXPOSED ANIMAL MODELS

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ABSTRACT

Using various key words, 195 research articles published between 2000-2017 in english were retrieved from the data base {Embase, Google Scholar, Medline (through Pubmed), Open J-gate, Scopus, Web of Science and Toxnet} for the meta-analysis of various serum and tissue biochemical parameters assessing renoprotective role of plant species in the gentamicin exposed animal models in comparison to controls (receiving only gentamicin). Odd ratios and Z values were found less than 1 for urea, creatinine, blood urea nitrogen (BUN), uric acid, lipid peroxidase (LPO) and malondialdehyde (MDA) and diamonds were on the left hand side of the null effect line of the forest plots, but their trends were opposite for the antioxidants (GSH, GPX, SOD and catalase) which led to conclude renoprotective role of plants in the gentamicin exposed animals. Funnel plot analysis revealed unbiasness in the publications while negative values of I^2 for all the parameters suggested all studies to be homogenous.

Key words: Antioxidants, BUN, creatinine, Gentamicin, kidney, meta-analysis, renoprotective plant species, urea

INTRODUCTION

Gentamicin is an aminoglycoside bestowed with a broad spectrum antimicrobial activity to both gram negative and gram positive infections (Turnidge 2003, Tam et al. 2006). The drug is highly charged and water soluble at physiologic pH (7.4), and therefore does not diffuse through biologic membranes (Morin et al. 1980). When gentamicin is either used for a longer period or at a slightly higher than recommended dose; 5% of it is retained in the epithelial cells of proximal convoluted tubules causing nephrotoxicity (Chaudhary and Paranjape 2013).

Yadav et al. (2017) reviewed renoprotective role of 151 plant species in the gentamicin exposed animals and identified species ameliorating kidney functions and oxidative stress. The conclusions were general and were not based on sample size and statistical analysis of findings presented for each parameter. These short comings were rectified in the meta-analysis 195 studies on renoprotective role of plant species presented in this review to derive at a point of estimate and identify patterns of findings, sources of disagreement and publication bias.

MATERIALS AND METHODS

Fixed effect model was used to evaluate nephroprotective ability of different doses of extracts/powder of various plant species in the gentamicin exposed animal models (hereafter referred to as treatment in the text) in comparison to controls receiving only gentamicin.

Various data bases were searched using nested and non-nested Boolean search terms like aminoglycosides, gentamicin induced nephrotoxicity, oxidative stress, MDA, LPO, kidney damage, renal injury, renal disorders, blood urea nitrogen, serum creatinin, serum urea, nephro/reno/curative/protective plant, nephroprotective activity, antioxidant defense enzymes, catalase and reduced glutathione.

Selection and eligibility criteria of observational studies included title and abstract screening and then full text screening to resolve agreement/disagreement of included studies. Only full length research articles published in english were considered for the meta-analysis of plant species providing nephroprotective ability in the gentamicin exposed animals. Conference abstracts, research articles published in non-english language and only abstracts were not considered in the meta-analysis. The studies lacking mean values were considered non-eligible and therefore, excluded from meta-analysis. The bibliographies of published studies helped to include missed studies relevant to the subject (Fig. A).

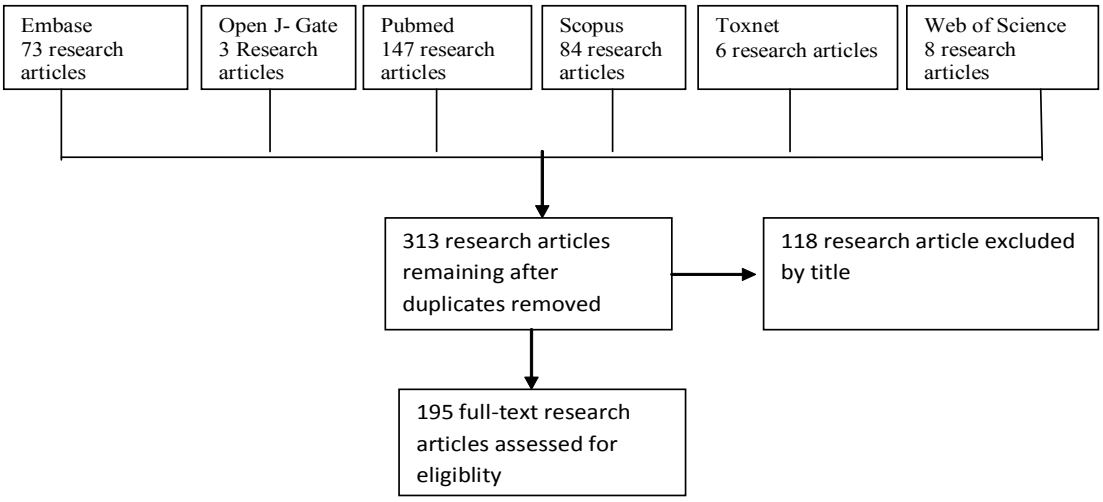

Fig. A. Flow diagram of literature search and study selection process

Data extraction

Data extracted from the eligible studies included sample size, gentamicin dose and its exposure period, types of nephroprotective herbal formulations, their dose, mode of treatment and data of serum biochemical parameters related to kidney function (urea, creatinine, BUN, uric acid) and tissue biochemistry of kidney for oxidative stress (LPO, MDA, catalase, GSH, SOD, GPx). Additional information included dose and time dependent amelioration in herbal treatments.

Data synthesis: We conducted a comprehensive meta analysis using mean values to display the trend of renal protection by different herbal formulations in gentamicin exposed animals (Hedge 2014) and calculated I^2 (Higgins et al. 2003) using nephroprotection according to type of extract, their dose and mode of treatment.

RESULTS AND DISCUSSION

Meta-analysis of studies under review revealed that herbal formulations reduced levels of urea, uric acid, BUN, creatinine in the serum; and of LPO and MDA in the kidney of gentamicin exposed animal models compared to controls receiving only gentamicin (Table 1). Antioxidant levels in kidney however, followed opposite trend (Table 1). The implications of these findings shall be improvement in the kidney functions (Silan et al. 2007) and reduction in free radicals induced injuries in the kidney (Gulcin 2006, Stojiljkovic et al. 2008). In nut shell, administration of herbs (extract/powder) reduced toxic effects of gentamicin in the kidney.

The values of Z, point estimate or odd ratio (RR) and CI were less than 1 for the overall study of urea, uric acid, creatinine, BUN, LPO and MDA (Table 1) and diamonds

Table 1. Values of point estimate, Z, Q and I^2 for various parameters.

Parameters	Effect size and 95% interval				Test of null (2-Tail)		Heterogeneity			
	No. of studies	Point estimate	Lower limit	Upper limit	Z- value	P-value	Q- value	Df (Q)	P-Value	I-Square
Creatinine	552	0.598	0.544	0.657	-10.696	0.0	76.058	551	1	-624.45%
Urea	404	0.645	0.607	0.685	-14.253	0.0	166.577	403	1	-141.93%
BUN	220	0.570	0.525	0.619	-13.323	0.0	119.348	219	1	-83.50%
Uric acid	101	0.698	0.583	0.836	-3.901	0.0	10.555	100	1	-847.4%
LPO	43	0.539	0.419	0.692	-4.830	0.0	19.290	42	0.999	-117.72%
MDA	106	0.645	0.562	0.740	-6.239	0.0	20.042	105	1	-423.90%
SOD	120	1.562	1.369	1.782	6.632	0.0	33.013	119	1	-260.46%
CAT	116	1.775	1.546	2.038	8.155	0.0	45.580	115	1	-152.30%
GSH	153	1.713	1.505	1.950	8.147	0.0	46.287	152	1	-228.39%
GP_X	40	1.480	1.175	1.865	3.328	0.0	11.021	39	1	-253.87%

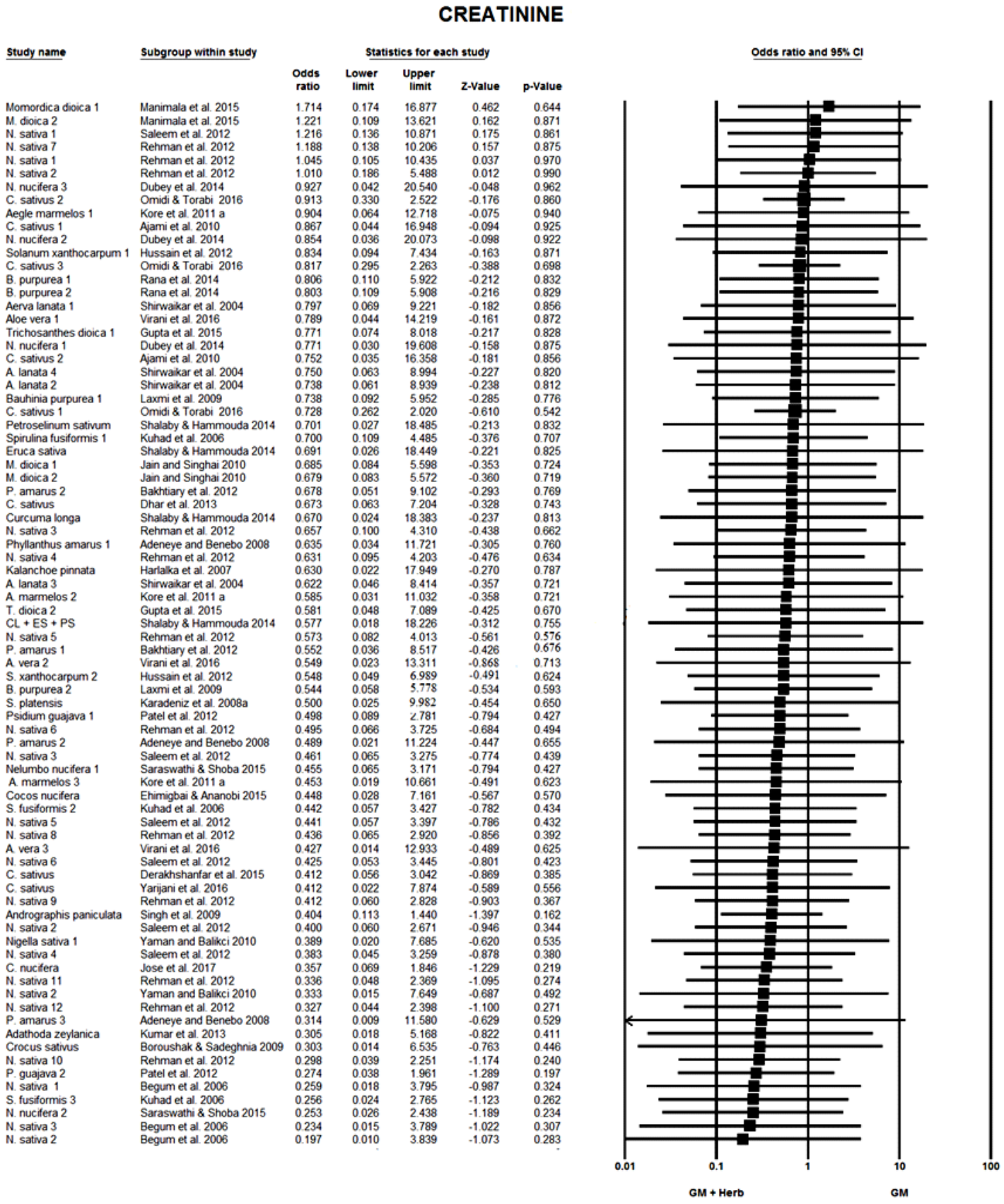

Fig.1a. Forest plot analysis of creatinine for nephroprotective species against gentamicin induced toxicity

CREATININE

Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
A. officinalis 3	Talebi et al. 2014	1.692	0.147	19.527	0.422	0.673
M. indica 10	Rad et al. 2011	1.481	0.120	18.239	0.307	0.759
R. emodi 2	Aslam et al. 2014	1.427	0.018	113.881	0.159	0.873
A. officinalis 2	Talebi et al. 2014	1.423	0.115	17.552	0.275	0.783
M. indica 7	Rad et al. 2011	1.077	0.030	39.273	0.040	0.968
Rhazya strica 1	Ali 2002	1.061	0.162	6.965	0.061	0.951
Althea officinalis 1	Talebi et al. 2014	1.038	0.073	14.861	0.028	0.978
M. oleifera 1	Quedraogo et al. 2013	1.010	0.315	3.239	0.017	0.987
M. oleifera 5	Quedraogo et al. 2013	1.000	0.312	3.207	0.000	1.000
P. fraternus 2	Kalyani et al. 2012	0.994	0.086	11.531	-0.005	0.996
R. emodi 6	Aslam et al. 2014	0.945	0.006	147.903	-0.022	0.982
M. oleifera 6	Quedraogo et al. 2013	0.937	0.293	2.997	-0.110	0.913
M. indica 3	Rad et al. 2011	0.923	0.022	38.144	-0.042	0.966
M. indica 5	Rad et al. 2011	0.923	0.022	38.144	-0.042	0.966
Cinnamomum zeylanicum 1	Tanomand & Najafian 2013	0.900	0.042	19.278	-0.067	0.946
M. oleifera 2	Quedraogo et al. 2013	0.892	0.279	2.855	-0.193	0.847
Rheum emodi 1	Aslam et al. 2014	0.874	0.007	115.429	-0.054	0.957
B. serrata 2	Alam et al. 2011	0.873	0.121	6.286	-0.135	0.893
R. emodi 4	Aslam et al. 2014	0.871	0.005	151.209	-0.052	0.958
Boswellia serrata 1	Alam et al. 2011	0.870	0.121	6.271	-0.138	0.890
G. biloba 1	Mansoor et al. 2015	0.788	0.105	5.933	-0.231	0.817
Elettaria cardamomum 1	Elkomy et al. 2015	0.783	0.089	6.885	-0.221	0.825
M. oleifera 4	Quedraogo et al. 2013	0.781	0.246	2.481	-0.419	0.675
R. emodi 5	Aslam et al. 2014	0.770	0.004	158.346	-0.096	0.923
Mangifera indica 1	Rad et al. 2011	0.769	0.016	37.611	-0.132	0.895
M. indica 9	Rad et al. 2011	0.769	0.016	37.611	-0.132	0.895
M. indica11	Rad et al. 2011	0.769	0.016	37.611	-0.132	0.895
Barringtonia acutangula	Mishra et al. 2014	0.761	0.072	7.997	-0.228	0.820
R. emodi 3	Aslam et al. 2014	0.755	0.004	159.778	-0.103	0.918
M. oleifera 7	Quedraogo et al. 2013	0.750	0.236	2.383	-0.488	0.626
M. indica 2	Rad et al. 2011	0.741	0.042	13.034	-0.205	0.837
C. zeylanicum 2	Tanomand & Najafian 2013	0.730	0.029	18.315	-0.191	0.848
Bacopa monneiri 1	Kannan et al. 2011	0.729	0.008	65.704	-0.138	0.891
P. alkekengi 2	Ahmad et al. 2010	0.722	0.072	7.198	-0.277	0.782
M. oleifera 3	Quedraogo et al. 2013	0.719	0.226	2.285	-0.560	0.576
R. emodi 7	Aslam et al. 2014	0.715	0.003	164.059	-0.121	0.904
M. indica 4	Rad et al. 2011	0.704	0.039	12.824	-0.237	0.812
Ocimum gratissimum 1	Ogundipe et al. 2016	0.688	0.194	2.431	-0.581	0.561
Phyllanthus fraternus1	Kalyani et al. 2012	0.687	0.048	9.807	-0.277	0.782
E. cardamomum 2	Elkomy et al. 2015	0.670	0.070	6.410	-0.348	0.728
O. gratissimum 2	Ogundipe et al. 2016	0.669	0.189	2.366	-0.624	0.533
B. monneiri 2	Kannan et al. 2011	0.667	0.007	67.251	-0.172	0.863
Ocimum sanctum	Kumar et al. 2014	0.660	0.042	10.387	-0.285	0.768
P. ginseng 1	Shin et al. 2014	0.650	0.001	724.975	-0.120	0.904
C. zeylanicum 3	Tanomand & Najafian 2013	0.650	0.023	18.805	-0.254	0.799
Physalis alkekengi 1	Ahmad et al. 2010	0.643	0.061	6.813	-0.367	0.714
Acacia senegal	Tahir et al. 2016	0.635	0.010	39.120	-0.216	0.829
P. ginseng	Karadeniz et al. 2008b	0.627	0.173	2.275	-0.710	0.478
P. fraternus 3	Kalyani et al. 2012	0.626	0.041	9.508	-0.338	0.736
M. oleifera 8	Quedraogo et al. 2013	0.625	0.196	1.991	-0.795	0.427
Panax ginseng	Kalkan et al. 2012	0.613	0.040	9.448	-0.351	0.726
T. portulacastrum	Balamurugan et al. 2009	0.612	0.022	17.137	-0.289	0.773
Trianthema portulacastrum	Vallabi and Elango 2015	0.607	0.048	7.682	-0.386	0.700
O. gratissimum 3	Ogundipe et al. 2016	0.606	0.171	2.148	-0.775	0.438
Oroxylum indicum	Mishra et al. 2014	0.589	0.048	7.158	-0.416	0.677
Moringa oleifera	Elazab and El-Habashi 2015	0.577	0.012	27.735	-0.278	0.781
Amorphophallus paeoniifolius 1	Madhurima 2010	0.557	0.038	8.156	-0.427	0.669
Terminalia chebula 1	Sivachandran & Hariharan 2012	0.537	0.025	11.455	-0.398	0.690
T. chebula 2	Sivachandran & Hariharan 2012	0.529	0.025	11.433	-0.406	0.685
G. biloba 2	Mansoor et al. 2015	0.513	0.056	4.705	-0.591	0.555
S. cordifolia 1	Makwana et al. 2012	0.513	0.076	3.474	-0.684	0.494
Vitex negundo	Mishra et al. 2014	0.498	0.037	6.767	-0.524	0.600
R. strica 2	Ali 2002	0.485	0.054	4.381	-0.645	0.519
P. ginseng	Qadir et al. 2011	0.482	0.022	10.782	-0.460	0.646
Piper cubeba 1	Zaid et al. 2012	0.474	0.054	4.175	-0.673	0.501
Pimpinella anisum	Ashtiyani et al. 2017	0.429	0.042	4.323	-0.719	0.472
M. indica 8	Rad et al. 2011	0.415	0.015	11.858	-0.514	0.607
M. indica 6	Rad et al. 2011	0.407	0.014	11.864	-0.522	0.602
M. indica 12	Rad et al. 2011	0.407	0.014	11.864	-0.522	0.602
S. cordifolia 2	Makwana et al. 2012	0.391	0.051	2.999	-0.904	0.366
A. paeonifolius 2	Madhurima 2010	0.381	0.019	7.602	-0.632	0.527
Sida cordifolia 1	Bhatia et al. 2012	0.373	0.043	3.214	-0.898	0.369
P. cubeba 4	Zaid et al. 2012	0.355	0.033	3.813	-0.855	0.393
P. cubeba 2	Zaid et al. 2012	0.343	0.031	3.782	-0.874	0.382
P. cubeba 3	Zaid et al. 2012	0.339	0.031	3.773	-0.879	0.379
P. ginseng 2	Shin et al. 2014	0.317	0.008	12.983	-0.607	0.544
Aristolochia indica	Arivazhagan and Vimalastalin 2014	0.300	0.014	6.653	-0.761	0.446
P. ginseng	Kalkan et al. 2012	0.290	0.009	9.242	-0.700	0.484
Gingko biloba	Naidu et al. 2000	0.273	0.015	4.850	-0.884	0.377
Tamarindus indica	Ullah et al. 2014b	0.269	0.024	2.982	-1.070	0.284
S. cordifolia 2	Bhatia et al. 2012	0.221	0.018	2.731	-1.177	0.239
S. cordifolia 3	Bhatia et al. 2012	0.183	0.013	2.667	-1.242	0.214
S. cordifolia 4	Bhatia et al. 2012	0.166	0.010	2.657	-1.269	0.205
R. strica 3	Ali 2002	0.133	0.005	3.774	-1.181	0.237

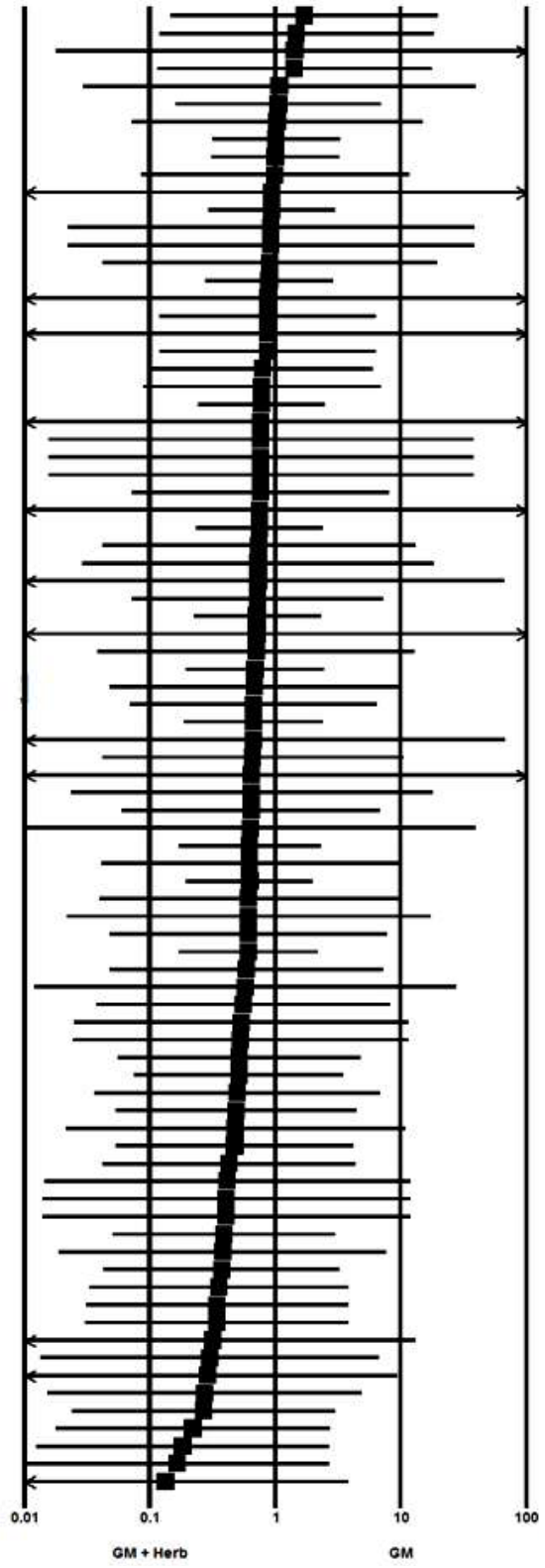

Fig. 1b. Forest plot analysis of creatinine for nephroprotective species against gentamicin induced toxicity

CREATININE

Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
M. tuberosa 3	Sujono et al. 2014	1.500	0.023	98.875	0.190	0.850
Myrmecodia tuberosa 1	Sujono et al. 2014	1.250	0.016	95.747	0.101	0.920
Tribulus terrestris 1	Kulkarni et al. 2012	1.186	0.149	9.471	0.161	0.872
M. tuberosa 5	Sujono et al. 2014	1.150	0.014	95.073	0.062	0.951
Mentha piperita 1	Ullah et al. 2013c	1.096	0.022	55.535	0.046	0.963
Verbascum thapsus 1	Pal et al. 2013	0.987	0.034	28.571	-0.007	0.994
V. thapsus 5	Pal et al. 2013	0.987	0.034	28.571	-0.007	0.994
V. thapsus 2	Pal et al. 2013	0.977	0.038	24.846	-0.014	0.989
V. thapsus 6	Pal et al. 2013	0.966	0.038	24.758	-0.021	0.983
Kigelia africana 1	Hoque et al. 2016	0.933	0.071	12.230	-0.053	0.958
V. thapsus 3	Pal et al. 2013	0.888	0.038	20.551	-0.074	0.941
B. diffusa 3	Sawardekar & Patel 2015	0.870	0.022	34.307	-0.075	0.941
S. nigrum	Priya and Venkatalakshmi 2011	0.861	0.093	7.997	-0.132	0.895
G. pictum 2	Srinivasan et al. 2015	0.860	0.077	9.595	-0.123	0.902
B. diffusa 1	Kulkarni et al. 2012	0.850	0.093	7.773	-0.144	0.886
Alangium salvifolium 1	Geetha & Ramarao 2014	0.849	0.067	10.791	-0.126	0.899
V. thapsus 7	Pal et al. 2013	0.847	0.035	20.278	-0.103	0.918
B. diffusa 1	Sawardekar & Patel 2015	0.841	0.021	34.170	-0.092	0.927
T. terrestris 2	Kulkarni et al. 2012	0.727	0.074	7.183	-0.273	0.785
Graptophyllum pictum 1	Srinivasan et al. 2015	0.725	0.059	8.931	-0.251	0.802
M. pudica 4	Geetha et al. 2015	0.724	0.026	20.130	-0.190	0.849
Foeniculum vulgare (FV) 1	Shaheen et al. 2014	0.708	0.030	16.785	-0.214	0.830
P. acidus 3	Vidya et al. 2013	0.704	0.075	6.587	-0.308	0.758
S. nigrum 4	Shaheen et al. 2014	0.689	0.028	16.703	-0.229	0.819
Bauhinia variegata	Prusty et al. 2012	0.688	0.035	13.409	-0.247	0.805
Solanum nigrum (SN) 2	Shaheen et al. 2014	0.670	0.027	16.626	-0.245	0.807
P. acidus 2	Vidya et al. 2013	0.660	0.068	6.378	-0.359	0.720
A. salvifolium 4	Geetha & Ramarao 2014	0.651	0.043	9.832	-0.310	0.757
FV + SN 5	Shaheen et al. 2014	0.642	0.025	16.522	-0.268	0.789
Phyllanthus acidus1	Vidya et al. 2013	0.640	0.065	6.284	-0.383	0.702
Mimosa pudica 1	Geetha et al. 2015	0.619	0.019	19.919	-0.271	0.787
F. vulgare 3	Shaheen et al. 2014	0.613	0.023	16.436	-0.291	0.771
T. purpurea 2	Jain et al. 2013	0.610	0.071	5.259	-0.450	0.653
G. pictum 3	Srinivasan et al. 2015	0.602	0.043	8.388	-0.377	0.706
V. thapsus 4	Pal et al. 2013	0.601	0.033	11.002	-0.343	0.732
K. africana 2	Hoque et al. 2016	0.597	0.034	10.421	-0.353	0.724
A. salvifolium 2	Geetha & Ramarao 2014	0.579	0.035	9.543	-0.382	0.702
P. granatum 2	Sadeghi et al. 2015	0.577	0.027	12.292	-0.352	0.725
Terminalia bellerica 1	Fatima and Sultana	0.576	0.054	6.099	-0.459	0.646
T. stans 1	Raju et al. 2011	0.575	0.068	4.849	-0.509	0.611
Boerhavia diffusa 1	Padmini and Kumar 2013	0.565	0.052	6.204	-0.467	0.641
Vitis vinifera	El-Ashmawy et al. 2006	0.553	0.014	21.681	-0.317	0.752
FV + SN 6	Shaheen et al. 2014	0.547	0.018	16.318	-0.348	0.728
B. diffusa 4	Sawardekar & Patel 2015	0.541	0.035	9.495	-0.437	0.662
V. thapsus 8	Pal et al. 2013	0.534	0.027	17.712	-0.410	0.682
M. pudica 2	Geetha et al. 2015	0.532	0.014	20.045	-0.341	0.733
T. stans 2	Raju et al. 2011	0.531	0.060	4.663	-0.571	0.568
T. stans 3	Raju et al. 2011	0.484	0.053	4.468	-0.639	0.523
Phyllanthus niruri 1	Gaddam et al. 2015	0.483	0.028	8.371	-0.500	0.617
K. senegalensis 2	El Badvi et al. 2012	0.475	0.024	9.528	-0.487	0.627
Tephrosia purpurea 1	Jain et al. 2013	0.471	0.048	4.663	-0.644	0.520
A. salvifolium 3	Geetha & Ramarao 2014	0.461	0.023	9.212	-0.507	0.612
P. niruri 2	Gaddam et al. 2015	0.459	0.025	8.299	-0.527	0.598
P. granatum 2	Boroushaki et al. 2014	0.457	0.026	8.120	-0.533	0.594
B. variegata 1	Sharma et al. 2011	0.457	0.046	4.486	-0.672	0.501
A. sativum 2	Nasri et al. 2013	0.412	0.022	7.621	-0.596	0.551
B. diffusa 2	Kulkarni et al. 2012	0.405	0.028	5.876	-0.663	0.507
B. diffusa 2	Sawardekar & Patel 2015	0.398	0.020	7.982	-0.602	0.547
T. bellerica 2	Fatima and Sultana	0.396	0.029	5.381	-0.696	0.486
P. granatum 1	Sadeghi et al. 2015	0.385	0.012	12.143	-0.542	0.587
P. granatum	Cekman et al. 2013	0.381	0.024	5.991	-0.687	0.492
Tecoma stans	Mohan et al. 2016	0.370	0.018	7.445	-0.650	0.516
M. pudica 3	Geetha et al. 2015	0.364	0.006	22.062	-0.482	0.630
B. variegata 3	Sharma et al. 2011	0.350	0.030	4.093	-0.836	0.403
M. piperita 2	Ullah et al. 2013c	0.337	0.017	6.832	-0.709	0.478
Khaya senegalensis 1	El Badvi et al. 2012	0.319	0.011	9.425	-0.662	0.508
B. diffusa 2	Padmini and Kumar 2013	0.313	0.018	5.580	-0.790	0.429
Cinnamomum tamala	Ullah et al. 2013a	0.301	0.029	3.082	-1.012	0.312
Allium sativum 1	Nasri et al. 2013	0.294	0.011	7.760	-0.733	0.464
Portulaca oleracea	Mouhamed and Elshafeey 2011	0.290	0.062	1.359	-1.571	0.116
M. tuberosa 2	Sujono et al. 2014	0.286	0.030	2.712	-1.091	0.275
B. variegata 2	Sharma et al. 2011	0.264	0.018	3.859	-0.974	0.330
M. piperita 3	Ullah et al. 2013c	0.251	0.022	2.934	-1.102	0.271
B. variegata 4	Sharma et al. 2011	0.212	0.012	3.808	-1.052	0.293
M. tuberosa 4	Sujono et al. 2014	0.173	0.013	2.372	-1.313	0.189
M. tuberosa 6	Sujono et al. 2014	0.102	0.004	2.412	-1.414	0.157
P. granatum 1	Boroushaki et al. 2014	0.057	0.000	36.968	-0.867	0.386

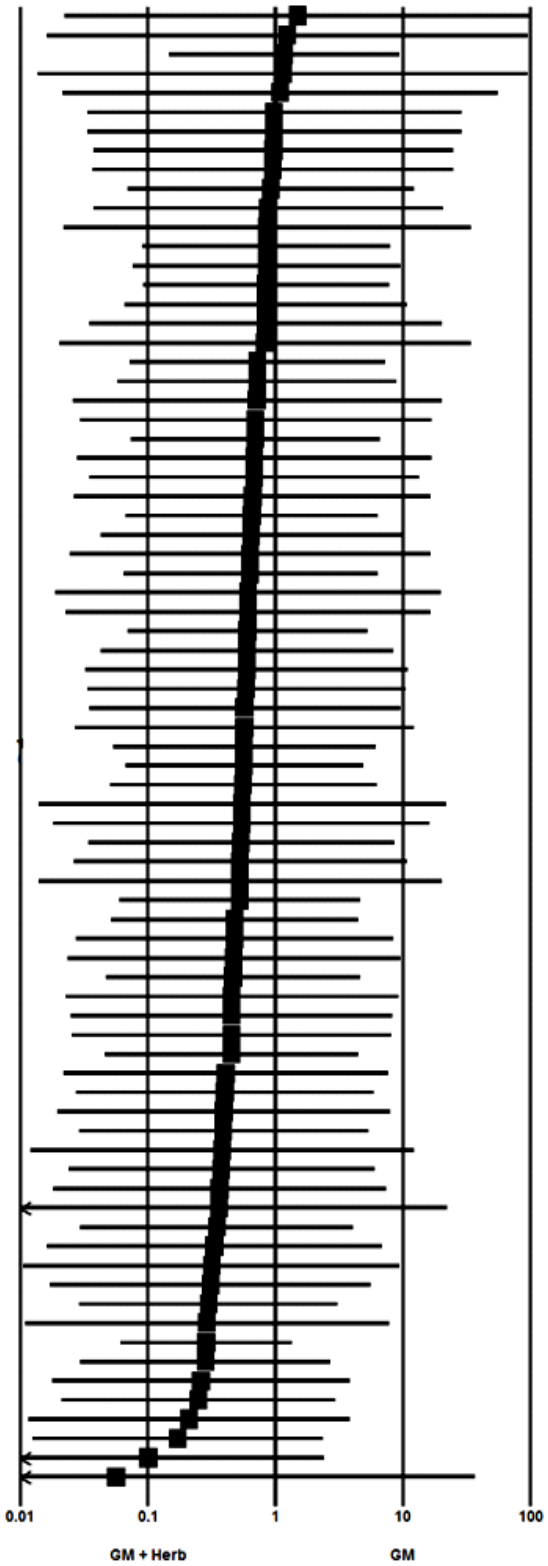

Fig.1c. Forest plot analysis of creatinine for nephroprotective species against gentamicin induced toxicity

CREATININE

Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Morus alba 1	Ullah et al. 2015	1.308	0.030	57.516	0.139	0.889
Citrullus colocynthis	Ullah et al. 2013b	0.968	0.161	5.827	-0.036	0.971
T. guineensis 3	Cyril et al. 2016	0.958	0.029	31.434	-0.024	0.981
Elaeocarpus ganitrus 1	Kakalij et al. 2014	0.953	0.119	7.661	-0.045	0.964
Aloe barbedensis 1	Chatterjee et al. 2012	0.874	0.163	4.695	-0.157	0.876
Trachyspermum ammi 1	Ishaq et al. 2015	0.867	0.034	22.048	-0.087	0.931
Delbergia sissoo 1	Saxena et al. 2016	0.864	0.033	22.749	-0.088	0.930
Calotropis procera 1	Javed et al. 2015	0.860	0.035	21.014	-0.092	0.926
T. ammi 2	Ishaq et al. 2015	0.856	0.033	21.981	-0.094	0.925
E. ganitrus 2	Kakalij et al. 2014	0.848	0.101	7.139	-0.151	0.880
T. guineensis 4	Cyril et al. 2016	0.847	0.023	30.806	-0.090	0.928
Citrus medica 1	Al-Yahya et al. 2015	0.825	0.178	3.820	-0.245	0.806
Trema guineensis 1	Cyril et al. 2016	0.819	0.022	30.691	-0.108	0.914
Cuscuta reflexa 1	Alamgeer et al. 2017	0.818	0.144	4.666	-0.226	0.821
Ferulago angulata 1	Valipour et al. 2016	0.809	0.108	6.055	-0.206	0.837
C. procera 2	Javed et al. 2015	0.806	0.031	20.705	-0.130	0.897
C. afer 2	Ezejiofor et al. 2014	0.773	0.218	2.743	-0.398	0.691
Beta vulgaris 1	El Gamal et al. 2014	0.770	0.173	3.433	-0.343	0.732
Trigonella foenum graceum 1	Kaur et al. 2016	0.769	0.159	3.716	-0.327	0.744
Ficus racemosa 1	Shivalinge and Vrushabendra2012	0.768	0.033	17.931	-0.164	0.870
D. sissoo 2	Saxena et al. 2016	0.750	0.025	22.164	-0.167	0.868
E. ganitrus 3	Kakalij et al. 2014	0.747	0.084	6.645	-0.262	0.794
Rosa damascene (RD) 1	Khaliq et al. 2014	0.736	0.084	6.432	-0.277	0.782
Costus afer 1	Ezejiofor et al. 2014	0.734	0.207	2.605	-0.479	0.632
F. racemosa 2	Shivalinge and Vrushabendra2012	0.723	0.030	17.709	-0.198	0.843
T. guineensis 2	Cyril et al. 2016	0.722	0.017	30.468	-0.170	0.865
C. medica 2	Al-Yahya et al. 2015	0.721	0.152	3.430	-0.411	0.681
E. divinorum 3	Feyissa et al. 2013	0.704	0.037	13.488	-0.233	0.816
Sonchus asper 1	Khan et al. 2011	0.703	0.100	4.931	-0.355	0.723
C. reflexa 2	Alamgeer et al. 2017	0.694	0.117	4.128	-0.401	0.688
Hemidesmus indicus 1	Kotnis et al. 2004	0.690	0.029	16.428	-0.229	0.819
Rubus ellipticus 1	Sharma & Kumar 2011	0.686	0.028	16.913	-0.231	0.818
E. divinorum 2	Feyissa et al. 2013	0.672	0.034	13.334	-0.261	0.794
C. afer 3	Ezejiofor et al. 2014	0.665	0.187	2.366	-0.630	0.529
Cynara scolymus 1	Khattab et al. 2016	0.661	0.197	2.224	-0.668	0.504
Cichorium intybus (CI) 3	Khaliq et al. 2014	0.660	0.072	6.076	-0.366	0.714
R. ellipticus 3	Sharma & Kumar 2011	0.657	0.026	16.802	-0.254	0.800
Pistacia khinjuk 1	Ghaedi et al. 2014	0.656	0.082	5.233	-0.398	0.691
F. angulata 2	Valipour et al. 2016	0.655	0.079	5.401	-0.393	0.694
I. aquatica	Sharmin et al. 2016	0.638	0.038	10.710	-0.312	0.755
R. ellipticus 2	Sharma & Kumar 2011	0.619	0.023	16.680	-0.285	0.775
F. angulata 3	Valipour et al. 2016	0.594	0.068	5.152	-0.473	0.636
RD + CI 5	Khaliq et al. 2014	0.592	0.061	5.765	-0.451	0.652
Euclea divinorum 1	Feyissa et al. 2013	0.576	0.026	12.950	-0.347	0.728
C. reflexa 3	Alamgeer et al. 2017	0.572	0.091	3.569	-0.596	0.551
C. scolymus 2	Khattab et al. 2016	0.571	0.169	1.935	-0.899	0.369
Carica papaya	Nale et al. 2012	0.562	0.026	12.184	-0.367	0.714
Jasminum grandiflorum 1	Venkataiah et al. 2013	0.559	0.039	7.915	-0.430	0.667
C. scolymus 3	Khattab et al. 2016	0.536	0.158	1.823	-0.998	0.318
B. vulgaris 2	El Gamal et al. 2014	0.530	0.110	2.558	-0.791	0.429
E. divinorum 5	Feyissa et al. 2013	0.528	0.022	12.820	-0.392	0.695
Enicostemma littorale	Bhatt et al. 2011	0.527	0.065	4.290	-0.599	0.549
Ipomoea digitata	Kalaiselvan et al. 2010	0.516	0.020	13.245	-0.399	0.690
C. intybus (CI) 4	Khaliq et al. 2014	0.509	0.048	5.402	-0.560	0.576
T. foenum graceum 2	Kaur et al. 2016	0.506	0.094	2.726	-0.793	0.428
Phoenix dactylifera 1	Al-Qarawi et al. 2008	0.480	0.018	13.054	-0.436	0.663
H. indicus 2	Kotnis et al. 2004	0.471	0.029	7.549	-0.532	0.594
E. divinorum 4	Feyissa et al. 2013	0.456	0.016	12.748	-0.462	0.644
M. alba 2	Ullah et al. 2015	0.439	0.027	7.046	-0.582	0.561
R. damascene (RD) 2	Khaliq et al. 2014	0.426	0.036	5.071	-0.675	0.500
A. barbedensis 2	Chatterjee et al. 2012	0.413	0.060	2.860	-0.896	0.370
P. khinjuk 2	Ghaedi et al. 2014	0.406	0.039	4.182	-0.757	0.449
Pedalium murex 1	Sreedevi et al. 2011	0.405	0.032	5.149	-0.697	0.486
C. scariosus 3	Gajjar et al. 2016	0.389	0.036	4.255	-0.774	0.439
J. grandiflorum 2	Venkataiah et al. 2013	0.383	0.020	7.338	-0.637	0.524
Echinodorus macrophyllus	Portella et al. 2012	0.364	0.009	15.231	-0.531	0.596
Sesamum indicum	Hsu et al. 2011	0.364	0.008	16.119	-0.523	0.601
RD + CI 6	Khaliq et al. 2014	0.358	0.027	4.839	-0.773	0.440
L. siceraria 2	Mahurkar et al. 2012	0.337	0.016	7.115	-0.699	0.484
Cyperus scariosus 1	Gajjar et al. 2016	0.330	0.027	4.090	-0.863	0.388
S. asper 2	Khan et al. 2011	0.324	0.031	3.399	-0.939	0.348
Lagenaria siceraria 1	Mahurkar et al. 2012	0.321	0.014	7.115	-0.719	0.472
M. alba 3	Ullah et al. 2015	0.316	0.032	3.131	-0.985	0.325
P. murex 2	Sreedevi et al. 2011	0.272	0.015	4.826	-0.887	0.375
T. foenum graceum 3	Kaur et al. 2016	0.261	0.037	1.837	-1.349	0.177
P. khinjuk 3	Ghaedi et al. 2014	0.250	0.017	3.715	-1.007	0.314
C. scariosus 4	Gajjar et al. 2016	0.229	0.013	3.956	-1.014	0.311
C. equisetifolia 2	El-Tantawy et al. 2013	0.223	0.007	7.096	-0.850	0.396
Casuarina equisetifolia 1	El-Tantawy et al. 2013	0.218	0.007	7.140	-0.855	0.392
C. scariosus 2	Gajjar et al. 2016	0.208	0.011	3.976	-1.043	0.297

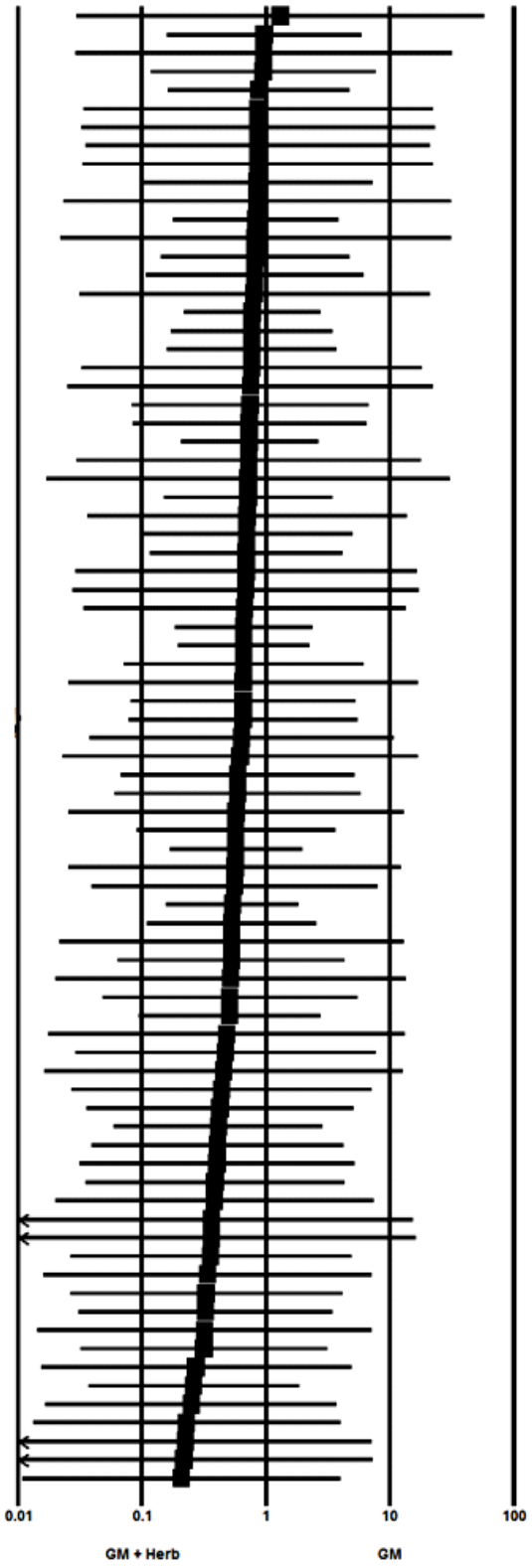

Fig. 1d. Forest plot analysis of creatinine for nephroprotective species against gentamicin induced toxicity

CREATININE

Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Citrus aurantium 1	Ullah et al. 2014a	1.135	0.023	55.829	0.064	0.949
Z. mays 4	Sepehri et al. 2009	1.111	0.084	14.751	0.080	0.936
Lantana camara	Vyas & Argal 2012	0.950	0.097	9.338	-0.044	0.965
Lavandula officinalis 1	Kalantar et al. 2016	0.941	0.141	6.294	-0.063	0.950
C. zambesicus 3	Okokon et al. 2011	0.909	0.289	2.864	-0.163	0.871
Ficus carica 1	Kore et al. 2011b	0.903	0.066	12.356	-0.076	0.939
Eryngium caucasicum 1	Eslami et al. 2011	0.886	0.325	2.411	-0.237	0.813
Entandrophragma angolense 9	Abou et al. 2016	0.871	0.213	3.554	-0.193	0.847
Gomphrena celosioides 5	Abou et al. 2016	0.845	0.206	3.464	-0.234	0.815
Allium cepa 1	Chinnala et al. 2017	0.837	0.155	4.523	-0.206	0.837
Cola nitida 1	Abou et al. 2016	0.837	0.204	3.434	-0.247	0.805
P. pinnata 2	Shirwaikar et al. 2003	0.829	0.053	12.895	-0.134	0.894
Pleurotus porrigens 1	Moghaddam et al. 2010	0.826	0.309	2.209	-0.380	0.704
Bryophyllum pinnata 1	Sule and Arhoghro 2016a	0.824	0.230	2.953	-0.297	0.766
Strychnos potatorum 1	Varghese et al. 2011	0.819	0.068	9.790	-0.158	0.875
B. pinnata 2	Sule and Arhoghro 2016a	0.813	0.227	2.913	-0.319	0.750
Pongamia pinnata 1	Shirwaikar et al. 2003	0.806	0.051	12.771	-0.153	0.879
Z. mays 3	Sepehri et al. 2009	0.800	0.050	12.790	-0.158	0.875
C. sativus 3	Pransanthi & Adikay 2016	0.800	0.062	10.279	-0.171	0.864
Asarum europaeum 1	Mamilla-pallai and Akkiraju 2015	0.770	0.120	4.949	-0.275	0.783
Volvariella volvacea 1	Kalava and Menon 2012	0.767	0.051	11.524	-0.192	0.848
E. angolense 11	Abou et al. 2016	0.761	0.183	3.165	-0.376	0.707
E. caucasicum 2	Eslami et al. 2011	0.751	0.273	2.067	-0.555	0.579
L. officinalis 2	Kalantar et al. 2016	0.735	0.101	5.361	-0.303	0.762
G. celosioides 7	Abou et al. 2016	0.727	0.174	3.045	-0.436	0.663
C. nitida 3	Abou et al. 2016	0.719	0.171	3.015	-0.452	0.651
Mucuna pruriens 1	Modi et al. 2008	0.712	0.056	9.112	-0.261	0.794
Z. mays 2	Sepehri et al. 2009	0.689	0.039	12.192	-0.254	0.799
Cucumis sativus 1	Pransanthi & Adikay 2016	0.682	0.043	10.904	-0.270	0.787
Croton zambesicus 1	Okokon et al. 2011	0.682	0.216	2.154	-0.652	0.514
Olea europaea 1	Abd El-Rehman 2016	0.672	0.052	8.609	-0.305	0.760
C. zambesicus 2	Okokon et al. 2011	0.659	0.209	2.083	-0.710	0.478
P. porrigens 2	Moghaddam et al. 2010	0.639	0.235	1.737	-0.877	0.380
Momordica charantia 1	Chawari et al. 2011	0.638	0.035	11.628	-0.304	0.761
Zea mays 1	Sepehri et al. 2009	0.630	0.033	11.914	-0.308	0.758
Curcuma longa	Negrette-Guzman et al. 2015	0.617	0.097	3.924	-0.512	0.609
M. pruriens 2	Modi et al. 2008	0.605	0.043	8.586	-0.372	0.710
S. potatorum 3	Varghese et al. 2011	0.590	0.040	8.629	-0.385	0.700
C. sativus 4	Pransanthi & Adikay 2016	0.588	0.038	9.207	-0.378	0.705
A. europaeum 2	Mamilla-pallai and Akkiraju 2015	0.583	0.082	4.153	-0.539	0.590
F. carica 2	Kore et al. 2011b	0.583	0.032	10.760	-0.363	0.717
S. potatorum 2	Varghese et al. 2011	0.581	0.039	8.585	-0.396	0.692
Terminalia ivorensis 1	Ansah et al. 2016	0.575	0.177	1.863	-0.923	0.356
C. sativus 2	Pransanthi & Adikay 2016	0.574	0.032	10.412	-0.375	0.708
Sida rhomboidea 1	Thounaojam et al. 2010	0.565	0.047	6.823	-0.449	0.653
P. granatum 2	Ali and Saeed 2012	0.555	0.071	4.329	-0.562	0.574
V. volvacea 2	Kalava and Menon 2012	0.548	0.029	10.488	-0.399	0.690
T. ivorensis 3	Ansah et al. 2016	0.521	0.160	1.693	-1.085	0.278
E. angolense 10	Abou et al. 2016	0.516	0.116	2.299	-0.868	0.385
P. dactylifera 3	Al-Qarawi et al. 2008	0.512	0.020	13.085	-0.405	0.686
O.europaea 2	Abd El-Rehman 2016	0.508	0.033	7.874	-0.484	0.628
C. nitida 2	Abou et al. 2016	0.507	0.113	2.270	-0.888	0.375
G. celosioides 6	Abou et al. 2016	0.507	0.113	2.270	-0.888	0.375
M. charantia 2	Chawari et al. 2011	0.500	0.022	11.137	-0.438	0.662
G. celosioides 8	Abou et al. 2016	0.499	0.111	2.240	-0.908	0.364
E. angolense 13	Abou et al. 2016	0.499	0.111	2.240	-0.908	0.364
C.nitida 4	Abou et al. 2016	0.490	0.109	2.210	-0.928	0.354
Benincasa hispida 1	Qadrie et al. 2013	0.467	0.032	6.767	-0.559	0.576
T. ivorensis 2	Ansah et al. 2016	0.466	0.143	1.519	-1.267	0.205
S. rhomboidea 2	Thounaojam et al. 2010	0.463	0.033	6.403	-0.575	0.566
A. cepa 2	Chinnala et al. 2017	0.459	0.070	3.019	-0.810	0.418
P. dactylifera 4	Al-Qarawi et al. 2008	0.455	0.016	13.056	-0.460	0.646
F. carica 3	Kore et al. 2011b	0.450	0.019	10.435	-0.498	0.619
Glycyrrhiza glabra	Yousef and Alkreathy 2016	0.440	0.026	7.563	-0.566	0.571
P. dactylifera 2	Al-Qarawi et al. 2008	0.431	0.014	13.086	-0.483	0.629
C. aurantium 2	Ullah et al. 2014a	0.429	0.026	7.015	-0.594	0.552
Houttuynia cordata 1	Kang et al. 2013	0.427	0.027	6.663	-0.607	0.544
Urtica dioca	Salih et al. 2015	0.426	0.046	3.917	-0.753	0.451
O. europaea 3	Abd El-Rehman 2016	0.415	0.023	7.579	-0.593	0.553
H. cordata 2	Kang et al. 2013	0.402	0.024	6.599	-0.638	0.523
Abutilon indicum 1	Jesurun & Lavakumar 2016	0.400	0.044	3.631	-0.814	0.416
L. officinalis 3	Kalantar et al. 2016	0.353	0.033	3.771	-0.862	0.389
Punica granatum 1	Ali and Saeed 2012	0.352	0.035	3.529	-0.887	0.375
F. carica	Ghafoor et al. 2015	0.344	0.005	22.397	-0.500	0.617
B. hispida 2	Qadrie et al. 2013	0.303	0.014	6.535	-0.763	0.446
A. indicum 2	Jesurun & Lavakumar 2016	0.267	0.022	3.182	-1.045	0.296
Saccharomyces cerevisiae	EL-Ghany et al. 2012	0.260	0.014	4.916	-0.899	0.369
Curcuma longa	EL-Ghany et al. 2012	0.248	0.013	4.911	-0.915	0.360
C. aurantium 3	Ullah et al. 2014a	0.246	0.021	2.921	-1.111	0.267
Apium graveolens	EL-Ghany et al. 2012	0.233	0.011	4.914	-0.937	0.349
Zingiber officinale	EL-Ghany et al. 2012	0.218	0.010	4.933	-0.958	0.338

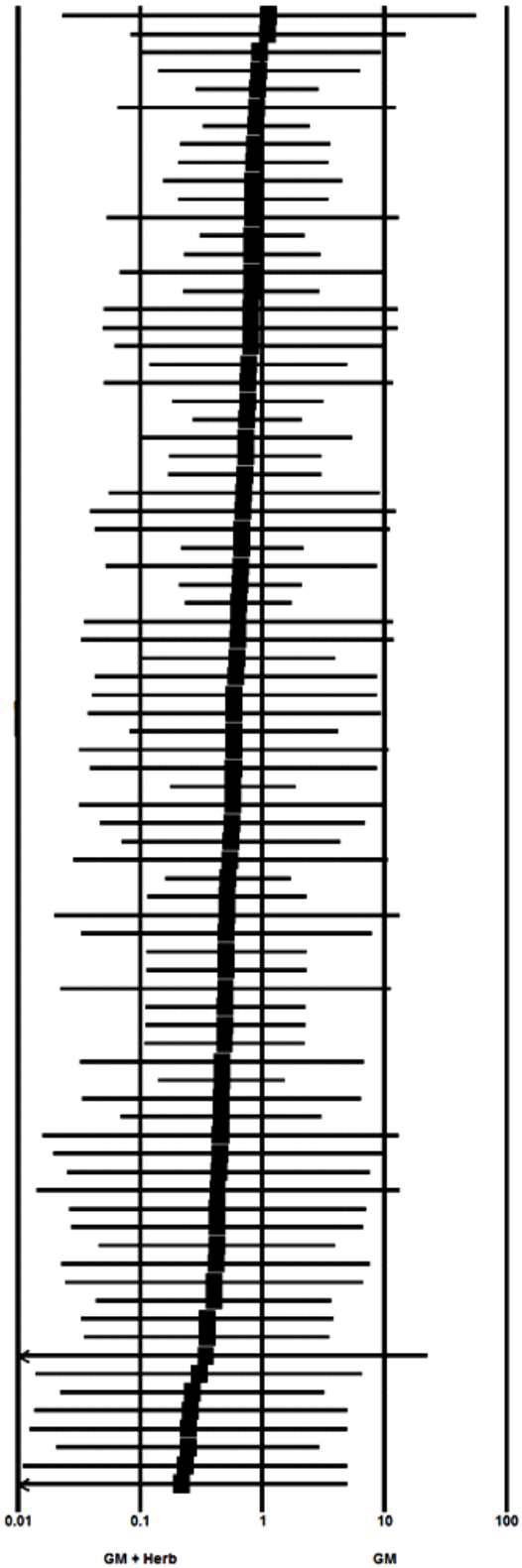

Fig. 1e. Forest plot analysis of creatinine for nephroprotective species against gentamicin induced toxicity

CREATININE

Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
H. spinosa 6	Bibu et al. 2010	1.388	0.225	8.566	0.353	0.724
H. spinosa 5	Bibu et al. 2010	1.067	0.016	69.954	0.030	0.976
Hygrophila spinosa 1	Bibu et al. 2010	1.044	0.016	69.901	0.020	0.984
H. spinosa 2	Bibu et al. 2010	1.011	0.148	6.882	0.011	0.991
G. kola 3	Komolafe et al. 2016	0.962	0.122	7.555	-0.037	0.971
Annona reticulata 1	Devi et al. 2016	0.944	0.040	22.553	-0.035	0.972
A. reticulata 3	Devi et al. 2016	0.901	0.039	20.806	-0.065	0.948
F. benghalensis 3	Mathew 2015	0.891	0.148	5.346	-0.126	0.899
Garcina kola 1	Komolafe et al. 2016	0.882	0.109	7.141	-0.117	0.907
E. alba 3	Dungca 2016	0.867	0.203	3.703	-0.193	0.847
Elephantopus scaber 1	Sahoo et al. 2012	0.836	0.138	5.081	-0.194	0.846
Lagersteoemia speciosa 1	http://shodhganga.inflibnet.ac.in	0.833	0.065	10.662	-0.140	0.889
Zingiber officinale 1	Rodrigues et al. 2014	0.829	0.041	16.738	-0.123	0.902
P. vera 2	Ehsani et al. 2017	0.825	0.035	19.615	-0.119	0.905
C. auriculata 2	Annie et al. 2005	0.806	0.051	12.771	-0.153	0.879
G. kola 4	Komolafe et al. 2016	0.799	0.095	6.713	-0.206	0.837
H. spinosa 3	Bibu et al. 2010	0.798	0.085	7.507	-0.197	0.844
Cassia auriculata 1	Annie et al. 2005	0.783	0.048	12.650	-0.172	0.863
A. reticulata 4	Devi et al. 2016	0.767	0.029	20.036	-0.159	0.874
A. reticulata 2	Devi et al. 2016	0.767	0.027	21.507	-0.156	0.876
G. kola 2	Komolafe et al. 2016	0.761	0.089	6.519	-0.249	0.803
Caralluma umbellata 1	Kumar & Sandhya 2014	0.750	0.059	9.585	-0.221	0.825
Daucus carota 1	Sodimbaku et al. 2016	0.744	0.068	8.126	-0.243	0.808
Z. officinale 2	Rodrigues et al. 2014	0.743	0.034	16.315	-0.189	0.850
Pistacia vera 1	Ehsani et al. 2017	0.722	0.027	19.091	-0.195	0.845
P. vera 3	Ehsani et al. 2017	0.711	0.027	19.048	-0.203	0.839
I. brachiata 6	Mathew 2015	0.684	0.108	4.342	-0.403	0.687
E. scaber 2	Sahoo et al. 2012	0.674	0.103	4.396	-0.412	0.681
H. spinosa 4	Bibu et al. 2010	0.660	0.046	9.576	-0.304	0.761
Macrothelypteris oligophlebia 1	Wu et al. 2012	0.621	0.206	1.867	-0.849	0.396
L. speciosa 2	http://shodhganga.inflibnet.ac.in	0.617	0.040	9.535	-0.345	0.730
Tephrosia purpuria 1	Jain et al. 2013	0.611	0.071	5.275	-0.448	0.654
C. umbellata 2	Kumar & Sandhya 2014	0.605	0.041	8.860	-0.367	0.713
Ficus benghalensis 1	Mathew 2015	0.603	0.092	3.953	-0.527	0.598
Z. officinale 3	Rodrigues et al. 2014	0.600	0.023	15.844	-0.306	0.760
Mangifera indica 3	http://shodhganga.inflibnet.ac.in	0.586	0.037	9.397	-0.377	0.706
T. bellerica 9	Mathew 2015	0.563	0.084	3.764	-0.592	0.554
Spathodea campanulata 1	Shanmukha et al. 2010	0.563	0.034	9.432	-0.400	0.689
Withania somnifera 1	Kushwaha et al. 2016	0.524	0.036	7.655	-0.473	0.637
D. carota 2	Sodimbaku et al. 2016	0.512	0.037	7.040	-0.500	0.617
C. viminalis 2	Sallem et al. 2016	0.509	0.028	9.305	-0.455	0.649
Eclipta alba 1	Dungca 2016	0.500	0.105	2.379	-0.851	0.384
Orthosiphon stamineus 1	Kannappan et al. 2010	0.492	0.066	3.666	-0.498	0.489
Aegle marmelos 1	Kalita et al. 2017	0.487	0.033	7.178	-0.524	0.600
M. oligophlebia 2	Wu et al. 2012	0.482	0.157	1.479	-1.276	0.202
T. purpuria 2	Jain et al. 2013	0.472	0.048	4.677	-0.642	0.521
Callestemon viminalis 1	Sallem et al. 2016	0.453	0.022	9.144	-0.517	0.605
Terminalia bellerica 7	Mathew 2015	0.448	0.062	3.215	-0.799	0.424
E. scaber 3	Sahoo et al. 2012	0.447	0.058	3.465	-0.770	0.441
M. indica 4	http://shodhganga.inflibnet.ac.in	0.432	0.021	8.882	-0.544	0.586
Ixor brachiata 4	Mathew 2015	0.424	0.058	3.104	-0.845	0.398
C. sinensis	Raheem et al. 2010	0.396	0.027	5.915	-0.671	0.502
S. campanulata 2	Shanmukha et al. 2010	0.394	0.017	8.981	-0.584	0.559
A. marmelos 2	Kalita et al. 2017	0.378	0.018	8.139	-0.621	0.534
F. benghalensis 2	Mathew 2015	0.370	0.048	2.853	-0.954	0.340
W. somnifera 2	Kushwaha et al. 2016	0.325	0.016	6.649	-0.730	0.466
C. sinensis	Veljkovic et al. 2015	0.321	0.129	0.797	-2.449	0.014
Sesbania grandiflora 1	Padamalochana and dhana rajan 2015	0.316	0.023	4.316	-0.864	0.388
A. marmelos 3	Kalita et al. 2017	0.305	0.011	8.563	-0.697	0.486
S. grandiflora 3	Padamalochana and dhana rajan 2015	0.302	0.021	4.282	-0.885	0.376
Camellia sinensis	Salem et al. 2010	0.295	0.035	2.521	-1.115	0.265
Morchella esculanta 1	Nitha and janardhan 2008	0.291	0.019	4.482	-0.885	0.376
H. spinosa 8	Bibu et al. 2010	0.288	0.009	9.162	-0.705	0.481
S. grandiflora 2	Padamalochana and dhana rajan 2015	0.288	0.020	4.251	-0.906	0.365
I. brachiata 5	Mathew 2015	0.286	0.033	2.475	-1.136	0.256
W. somnifera 3	Kushwaha et al. 2016	0.273	0.013	5.879	-0.829	0.407
E. alba 2	Dungca 2016	0.254	0.067	0.959	-2.022	0.043
O. stamineus 3	Kannappan et al. 2010	0.243	0.021	2.773	-1.138	0.255
H. spinosa 7	Bibu et al. 2010	0.239	0.010	5.926	-0.873	0.383
O. stamineus 2	Kannappan et al. 2010	0.239	0.021	2.761	-1.147	0.251
E. alba 4	Dungca 2016	0.220	0.057	0.850	-2.196	0.028
M. esculanta 2	Nitha and janardhan 2008	0.218	0.011	4.441	-0.990	0.322
T. bellerica 8	Mathew 2015	0.209	0.020	2.151	-1.316	0.188
Sphaeranthus indicus 1	Mathew et al. 2009	0.207	0.021	1.999	-1.362	0.173
Glycine max 1	Ekor et al. 2006	0.189	0.043	0.831	-2.206	0.027
G. max 2	Ekor et al. 2006	0.189	0.043	0.831	-2.206	0.027
S.indicus 2	Mathew et al. 2009	0.141	0.011	1.855	-1.489	0.136

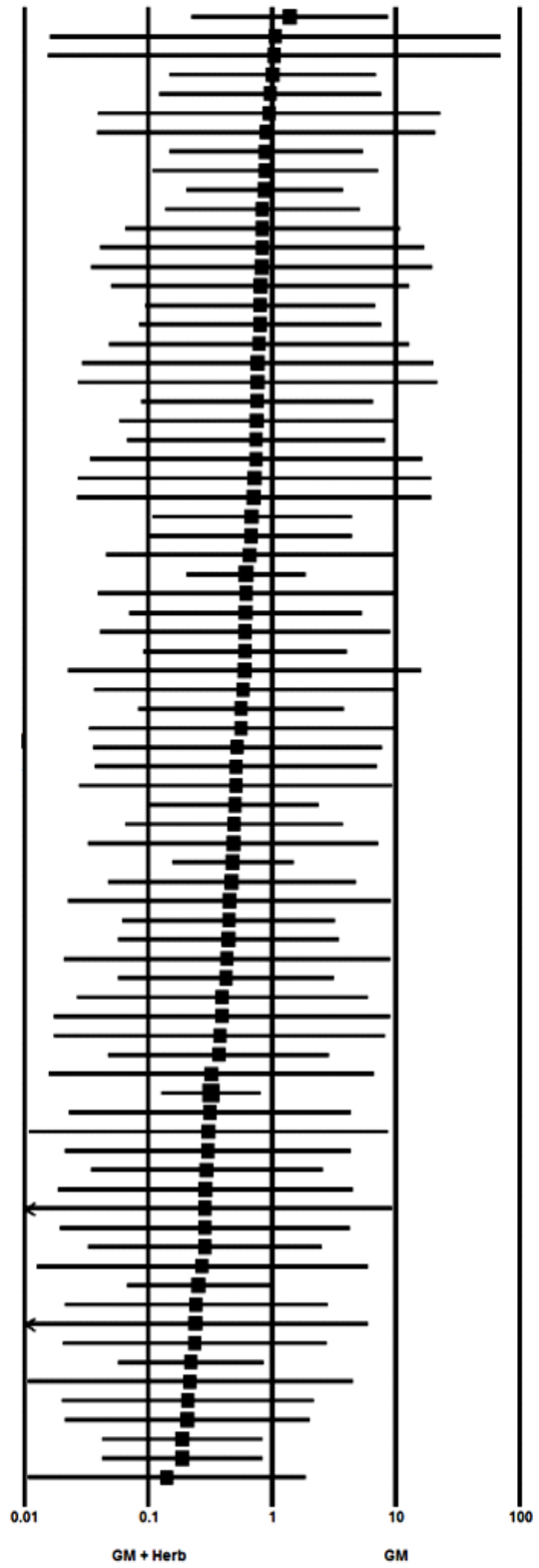

Fig. 1f. Forest plot analysis of creatinine for nephroprotective species against gentamicin induced toxicity

CREATININE

Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
C. nurvala (CN) 51	Meher et al. 2016	1.000	0.040	24.837	0.000	1.000
T. terrestris (TT) 55	Meher et al. 2016	1.000	0.040	24.837	0.000	1.000
C. nurvala (CN) 57	Meher et al. 2016	1.000	0.040	24.837	0.000	1.000
C. nurvala (CN)33	Meher et al. 2016	0.971	0.088	10.709	-0.024	0.981
C. nurvala (CN) 45	Meher et al. 2016	0.969	0.064	14.655	-0.023	0.982
C. nurvala (CN) 21	Meher et al. 2016	0.953	0.094	9.695	-0.041	0.968
C. nurvala (CN) 27	Meher et al. 2016	0.948	0.085	10.576	-0.043	0.966
T. terrestris (TT)31	Meher et al. 2016	0.948	0.085	10.576	-0.043	0.966
T. terrestris (TT) 49	Meher et al. 2016	0.941	0.036	24.420	-0.036	0.971
C. nurvala (CN) 52	Meher et al. 2016	0.941	0.036	24.420	-0.036	0.971
T. terrestris (TT) 56	Meher et al. 2016	0.941	0.036	24.420	-0.036	0.971
C. nurvala (CN) 58	Meher et al. 2016	0.941	0.036	24.420	-0.036	0.971
T. terrestris (TT)19	Meher et al. 2016	0.938	0.091	9.608	-0.054	0.957
T. terrestris (TT) 38	Meher et al. 2016	0.938	0.061	14.454	-0.046	0.963
C. nurvala (CN) 39	Meher et al. 2016	0.938	0.061	14.454	-0.046	0.963
T. terrestris (TT) 43	Meher et al. 2016	0.938	0.061	14.454	-0.046	0.963
T. terrestris (TT) 61	Meher et al. 2016	0.938	0.023	37.895	-0.034	0.973
C. nurvala (CN) 63	Meher et al. 2016	0.938	0.023	37.895	-0.034	0.973
C. nurvala (CN) 64	Meher et al. 2016	0.938	0.023	37.895	-0.034	0.973
T. terrestris (TT) 67	Meher et al. 2016	0.938	0.023	37.895	-0.034	0.973
T. terrestris (TT) 68	Meher et al. 2016	0.938	0.023	37.895	-0.034	0.973
C. nurvala (CN) 69	Meher et al. 2016	0.938	0.023	37.895	-0.034	0.973
C. nurvala (CN) 70	Meher et al. 2016	0.938	0.023	37.895	-0.034	0.973
C. nurvala (CN) 15	Meher et al. 2016	0.932	0.091	9.579	-0.059	0.953
TT + CN 47	Meher et al. 2016	0.922	0.059	14.354	-0.058	0.954
T. terrestris (TT) 25	Meher et al. 2016	0.920	0.081	10.411	-0.068	0.946
C. nurvala (CN) 34	Meher et al. 2016	0.920	0.081	10.411	-0.068	0.946
C. nurvala (CN) 16	Meher et al. 2016	0.911	0.088	9.464	-0.078	0.938
T. terrestris (TT) 37	Meher et al. 2016	0.898	0.057	14.207	-0.076	0.939
C. nurvala (CN) 46	Meher et al. 2016	0.898	0.057	14.207	-0.076	0.939
T. terrestris (TT) 50	Meher et al. 2016	0.894	0.033	24.111	-0.067	0.947
T. terrestris (TT)32	Meher et al. 2016	0.885	0.077	10.215	-0.098	0.922
TT + CN 59	Meher et al. 2016	0.882	0.032	24.038	-0.074	0.941
C. nurvala (CN) 28	Meher et al. 2016	0.862	0.074	10.085	-0.118	0.906
T. terrestris (TT)13	Meher et al. 2016	0.859	0.080	9.179	-0.125	0.900
C. nurvala (CN) 22	Meher et al. 2016	0.859	0.080	9.179	-0.125	0.900
C. nurvala (CN) 40	Meher et al. 2016	0.859	0.053	13.966	-0.107	0.915
T. terrestris (TT)14	Meher et al. 2016	0.844	0.078	9.094	-0.140	0.889
T. terrestris (TT)44	Meher et al. 2016	0.844	0.051	13.872	-0.119	0.905
T. terrestris (TT)20	Meher et al. 2016	0.833	0.077	9.038	-0.150	0.881
TT + CN 23	Meher et al. 2016	0.833	0.077	9.038	-0.150	0.881
C. nurvala (CN) 9	Meher et al. 2016	0.830	0.091	7.566	-0.162	0.869
Crataeva nurvala (CN) 3	Meher et al. 2016	0.813	0.088	7.496	-0.183	0.855
C. nurvala (CN) 4	Meher et al. 2016	0.809	0.088	7.469	-0.188	0.851
T. terrestris (TT) 7	Meher et al. 2016	0.809	0.088	7.459	-0.188	0.851
Tribulus terrestris (TT) 1	Meher et al. 2016	0.787	0.084	7.352	-0.210	0.834
C. nurvala (CN)10	Meher et al. 2016	0.787	0.084	7.352	-0.210	0.834
TT + CN 17	Meher et al. 2016	0.781	0.070	8.760	-0.200	0.841
TT + CN 24	Meher et al. 2016	0.781	0.070	8.760	-0.200	0.841
T. terrestris (TT)26	Meher et al. 2016	0.776	0.063	9.611	-0.198	0.843
C. nurvala (CN) 35	Meher et al. 2016	0.770	0.062	9.580	-0.203	0.839
T. terrestris (TT) 8	Meher et al. 2016	0.766	0.081	7.246	-0.233	0.816
TT + CN 11	Meher et al. 2016	0.766	0.081	7.246	-0.233	0.816
T. terrestris (TT) 2	Meher et al. 2016	0.757	0.080	7.204	-0.242	0.809
TT + CN 53	Meher et al. 2016	0.753	0.024	23.375	-0.162	0.871
TT + CN 60	Meher et al. 2016	0.753	0.024	23.375	-0.162	0.871
TT + CN 5	Meher et al. 2016	0.745	0.078	7.141	-0.256	0.798
TT + CN 12	Meher et al. 2016	0.740	0.077	7.120	-0.260	0.795
T. terrestris (TT) 62	Meher et al. 2016	0.719	0.014	37.476	-0.164	0.870
TT + CN 41	Meher et al. 2016	0.703	0.038	13.089	-0.236	0.813
TT + CN 71	Meher et al. 2016	0.703	0.013	37.530	-0.174	0.862
TT + CN 18	Meher et al. 2016	0.667	0.054	8.174	-0.317	0.751
TT + CN 48	Meher et al. 2016	0.664	0.034	12.901	-0.270	0.787
Coriandrum sativum 1	Lakhera et al. 2015	0.657	0.083	5.232	-0.397	0.692
TT + CN 72	Meher et al. 2016	0.656	0.011	37.791	-0.204	0.839
TT + CN 6	Meher et al. 2016	0.638	0.061	6.627	-0.376	0.707
TT + CN 65	Meher et al. 2016	0.625	0.010	38.065	-0.224	0.823
TT + CN 29	Meher et al. 2016	0.621	0.044	8.823	-0.352	0.725
TT + CN 36	Meher et al. 2016	0.615	0.043	8.796	-0.358	0.720
TT + CN 30	Meher et al. 2016	0.489	0.029	8.276	-0.496	0.620
TT + CN 66	Meher et al. 2016	0.484	0.006	40.883	-0.320	0.749
C. sativum 2	Lakhera et al. 2015	0.457	0.048	4.311	-0.684	0.494
TT + CN 54	Meher et al. 2016	0.365	0.005	25.959	-0.464	0.643
TT + CN 42	Meher et al. 2016	0.328	0.008	12.808	-0.596	0.551
		0.598	0.544	0.657	-10.696	0.000

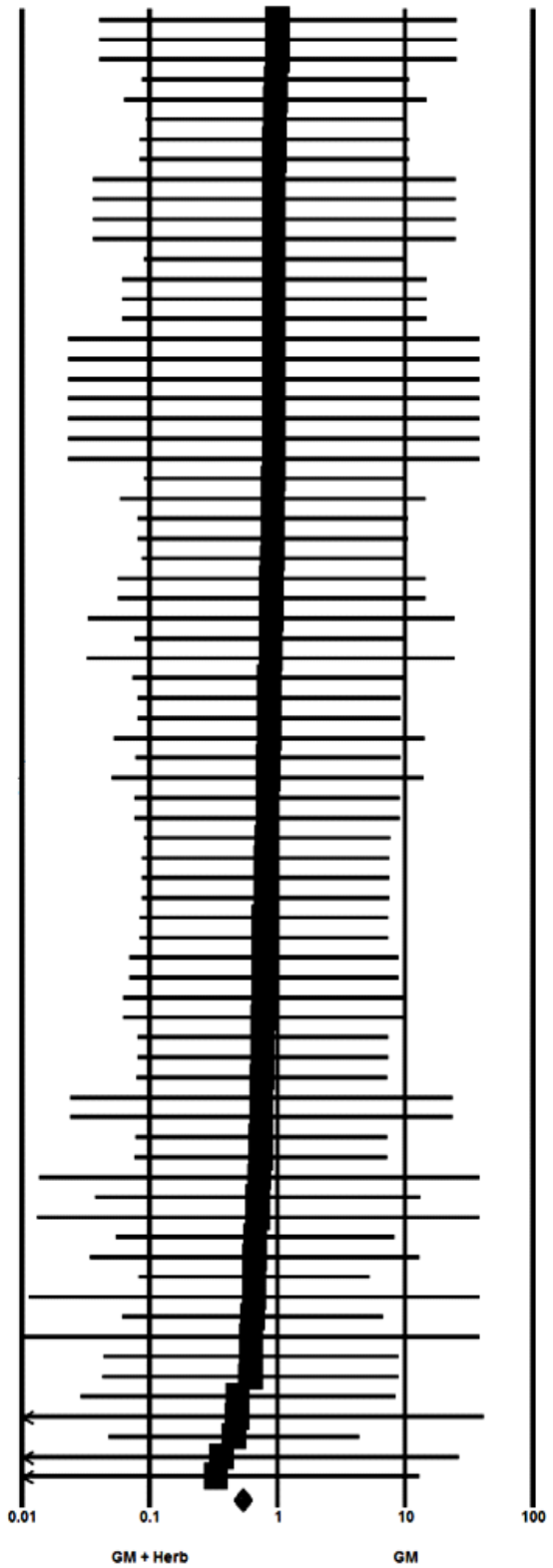

Fig. 1g. Forest plot analysis of creatinine for nephroprotective species against gentamicin induced toxicity

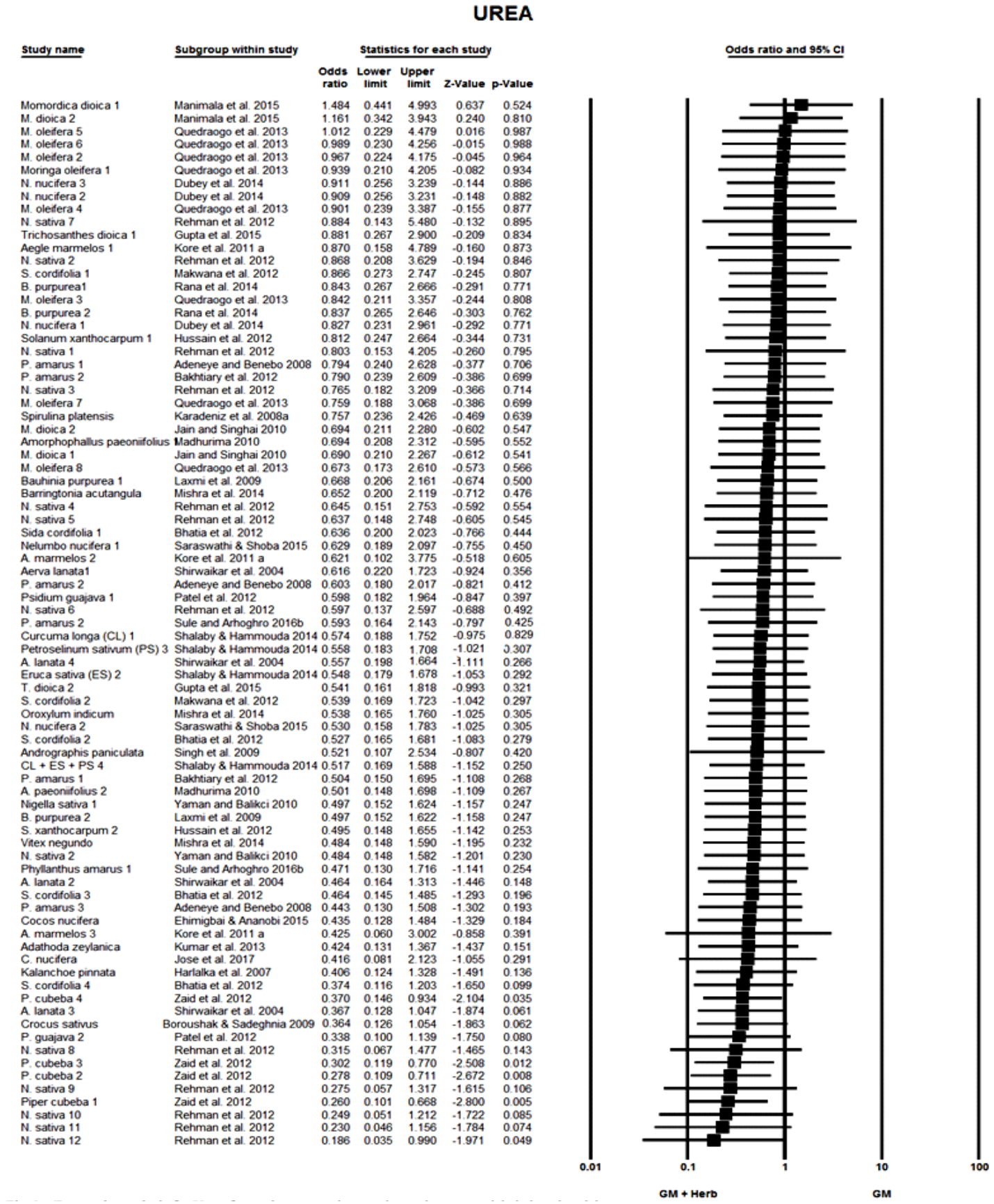

Fig. 2a. Forest plot analysis of urea for nephroprotective species against gentamicin induced toxicity

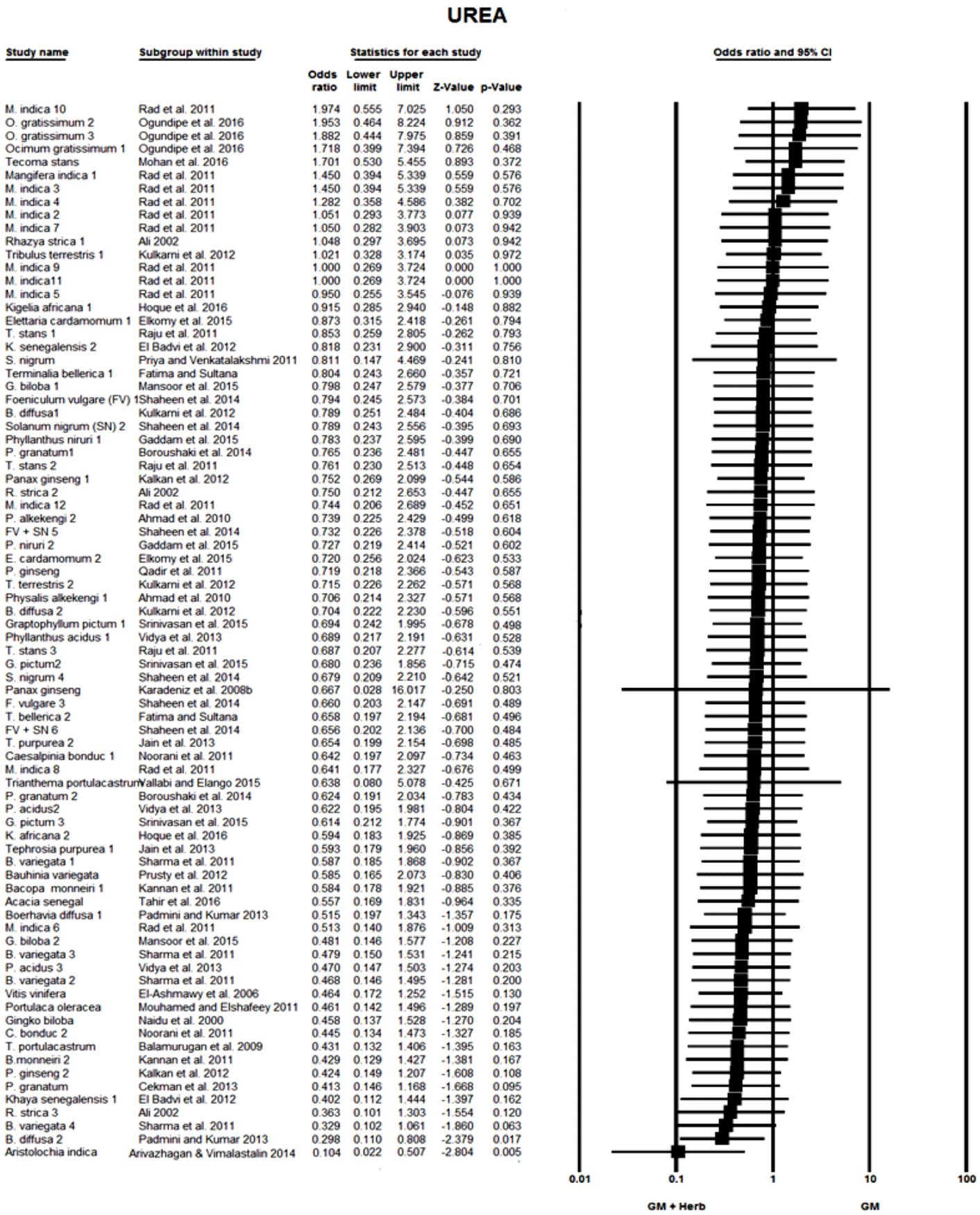

Fig. 2b. Forest plot analysis of urea for nephroprotective species against gentamicin induced toxicity

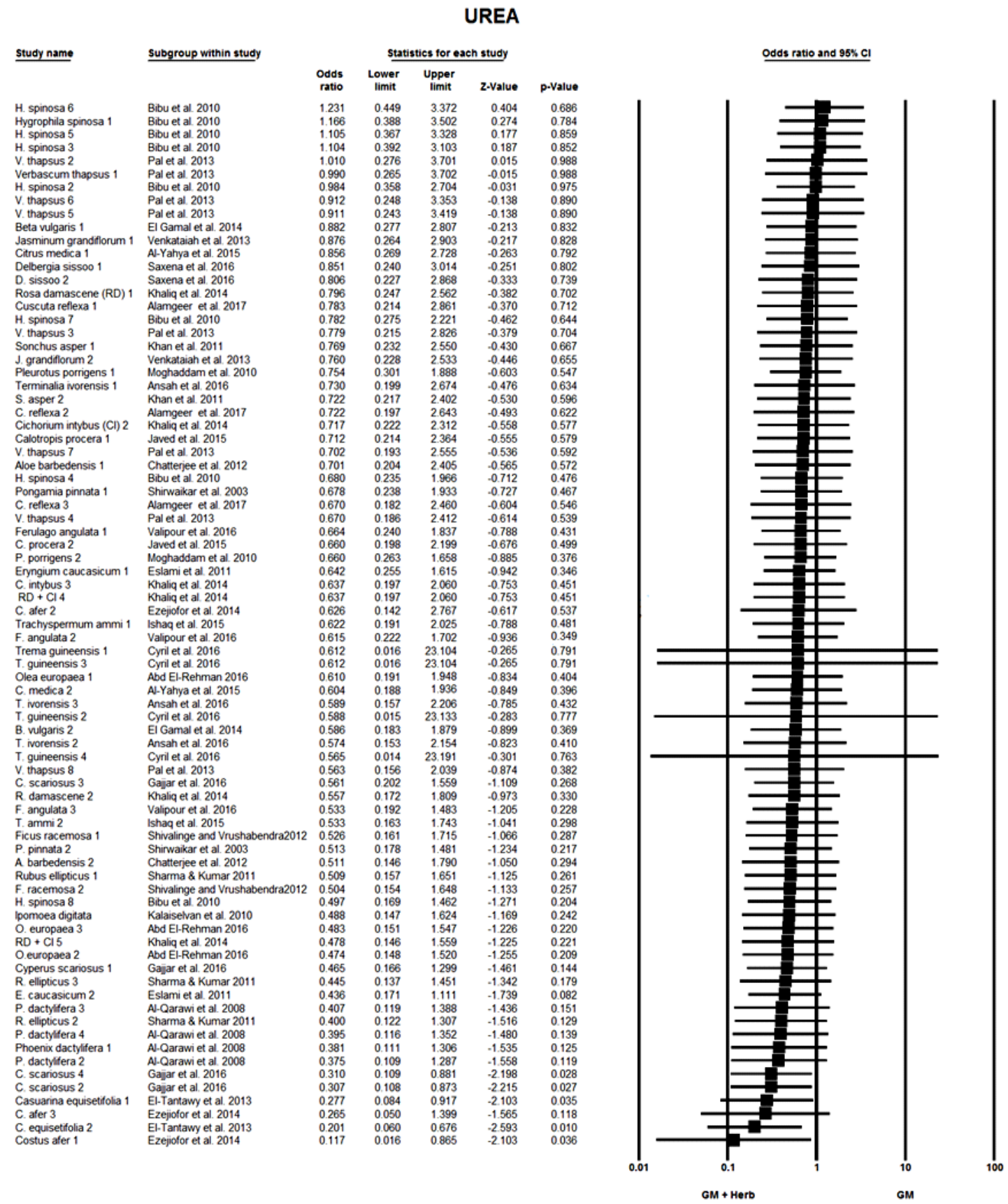

Fig. 2c. Forest plot analysis of urea for nephroprotective species against gentamicin induced toxicity

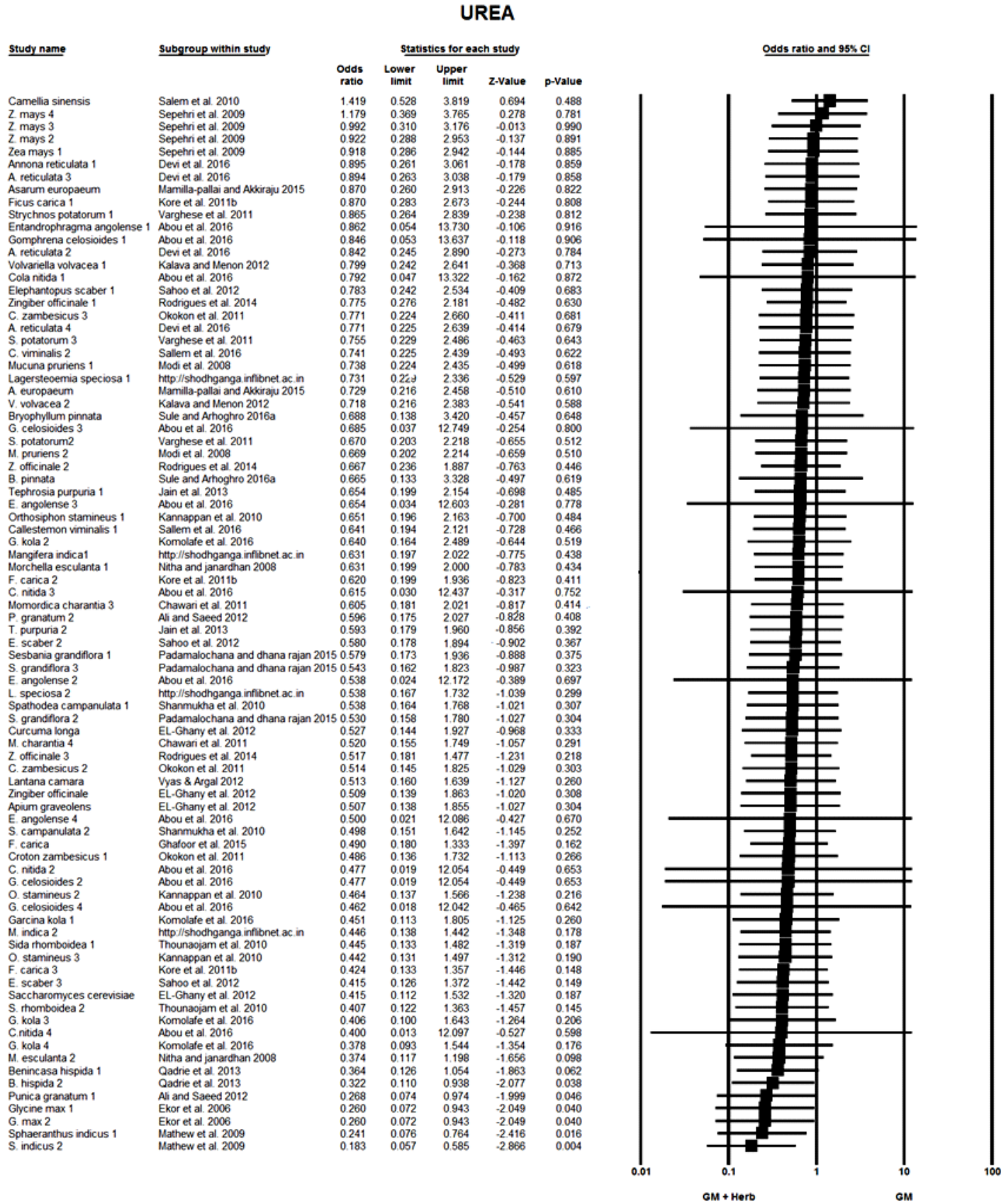

Fig. 2d. Forest plot analysis of urea for nephroprotective species against gentamicin induced toxicity

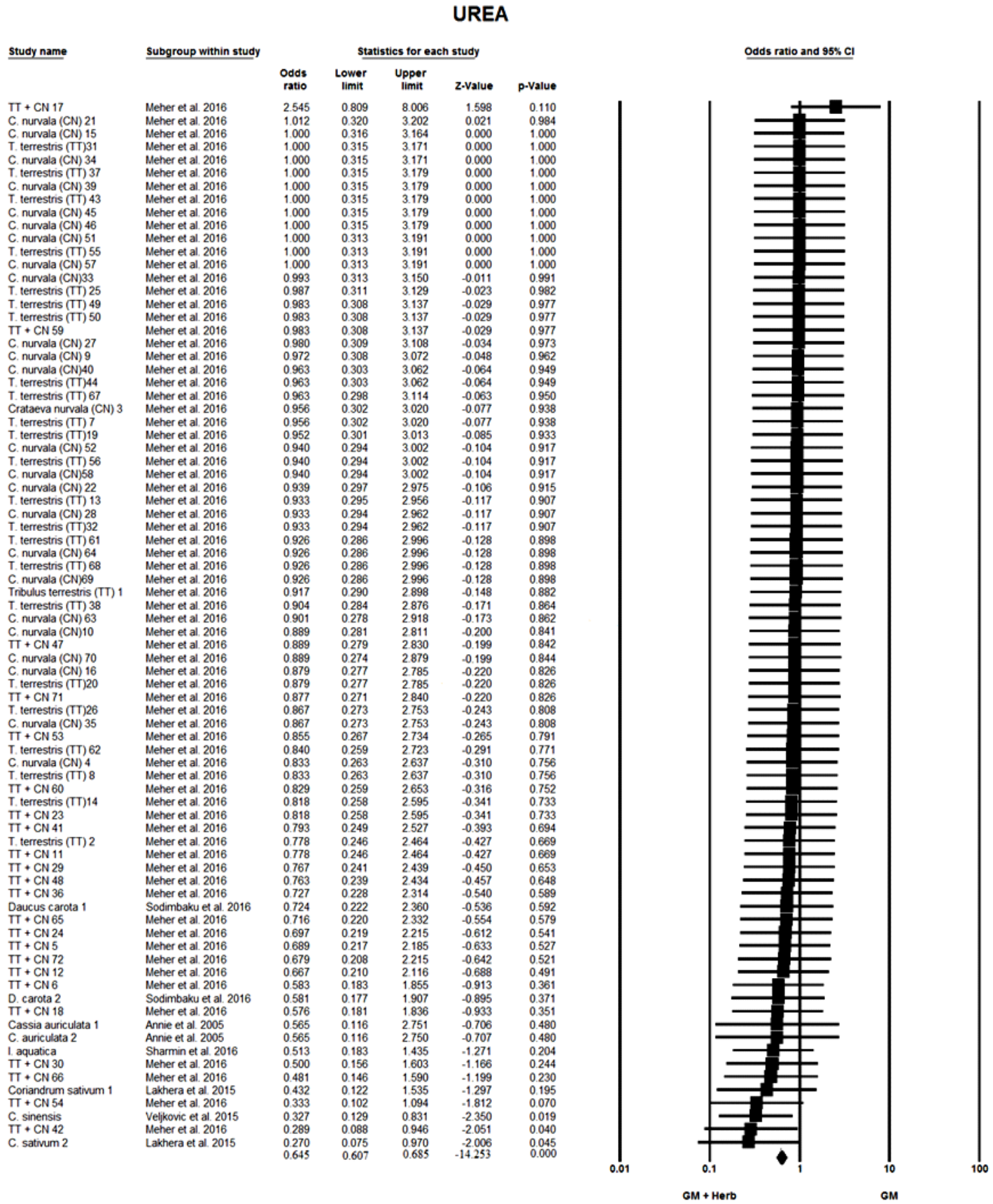

Fig. 2e. Forest plot analysis of urea for nephroprotective species against gentamicin induced toxicity

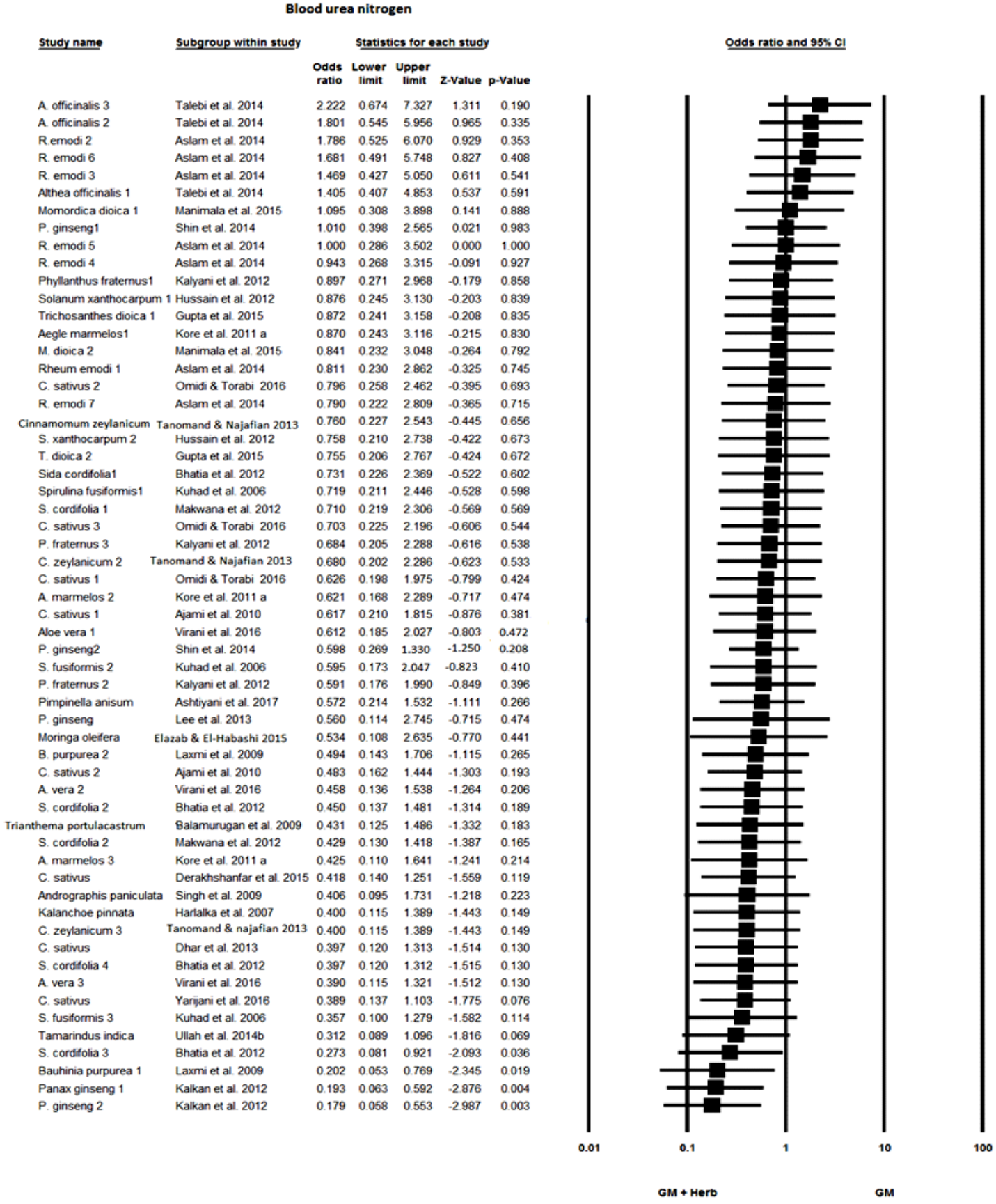

Fig. 3a. Forest plot analysis of BUN for nephroprotective species against gentamicin induced toxicity

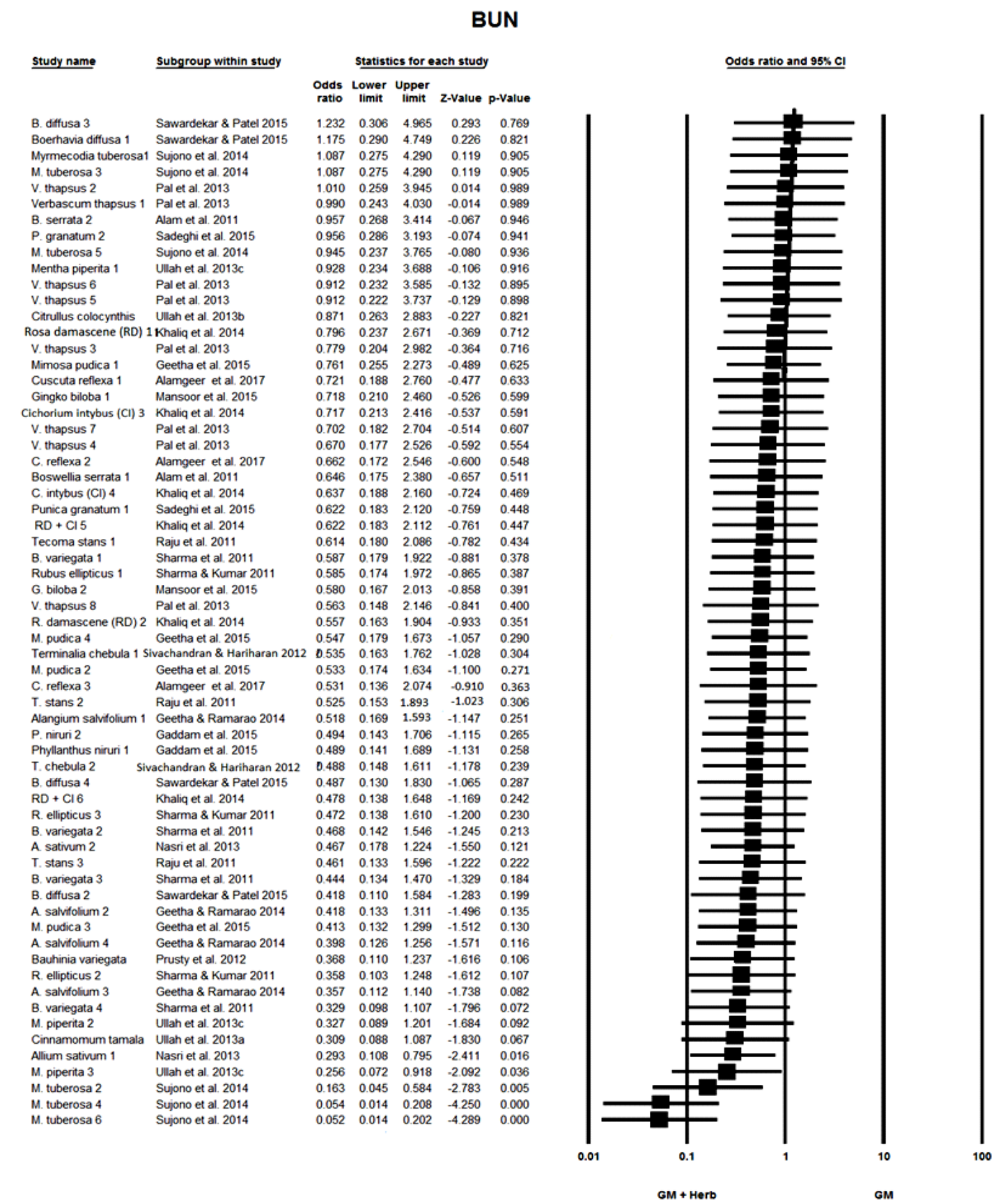

Fig. 3b. Forest plot analysis of BUN for nephroprotective species against gentamicin induced toxicity

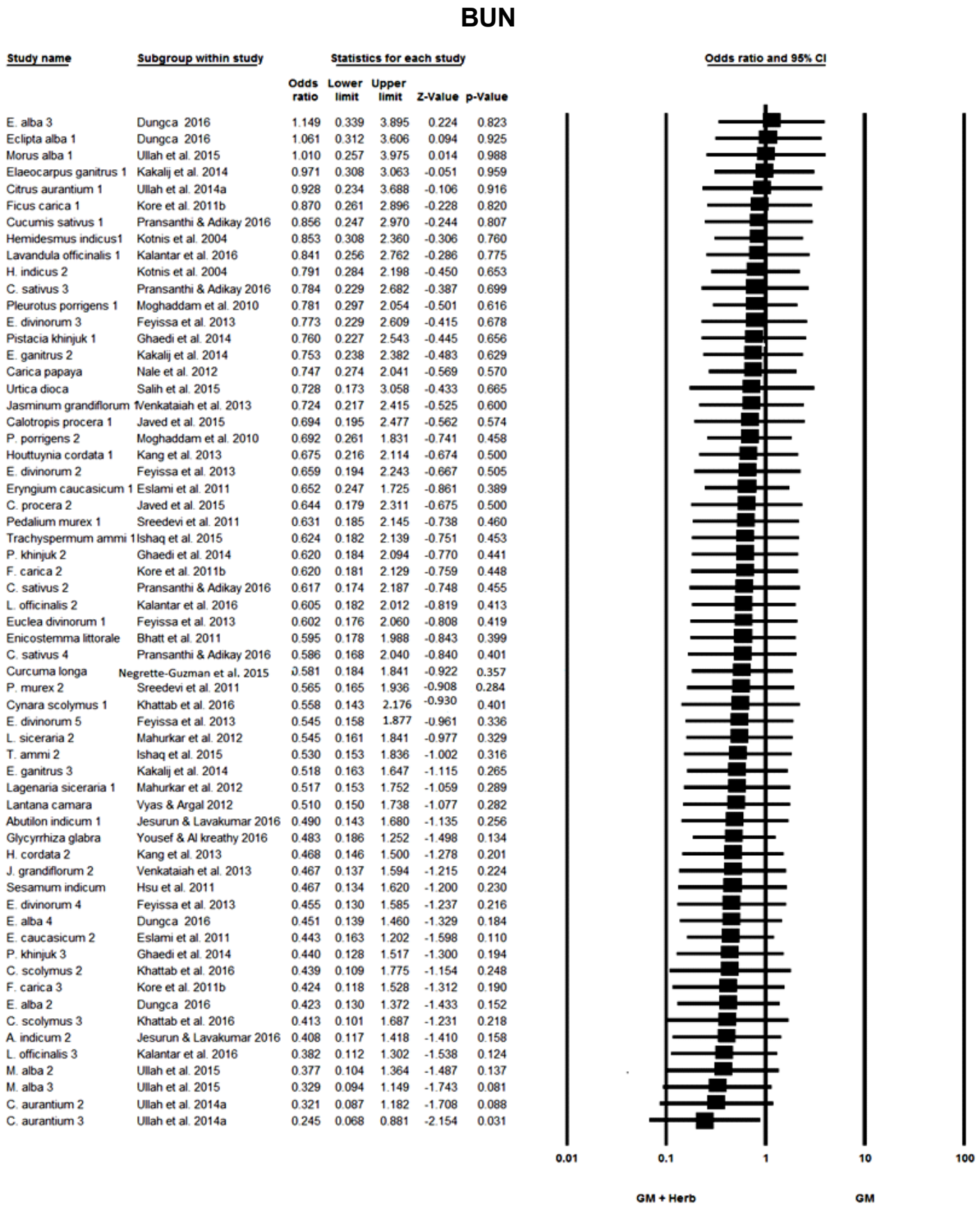

Fig. 3c. Forest plot analysis of BUN for nephroprotective species against gentamicin induced toxicity

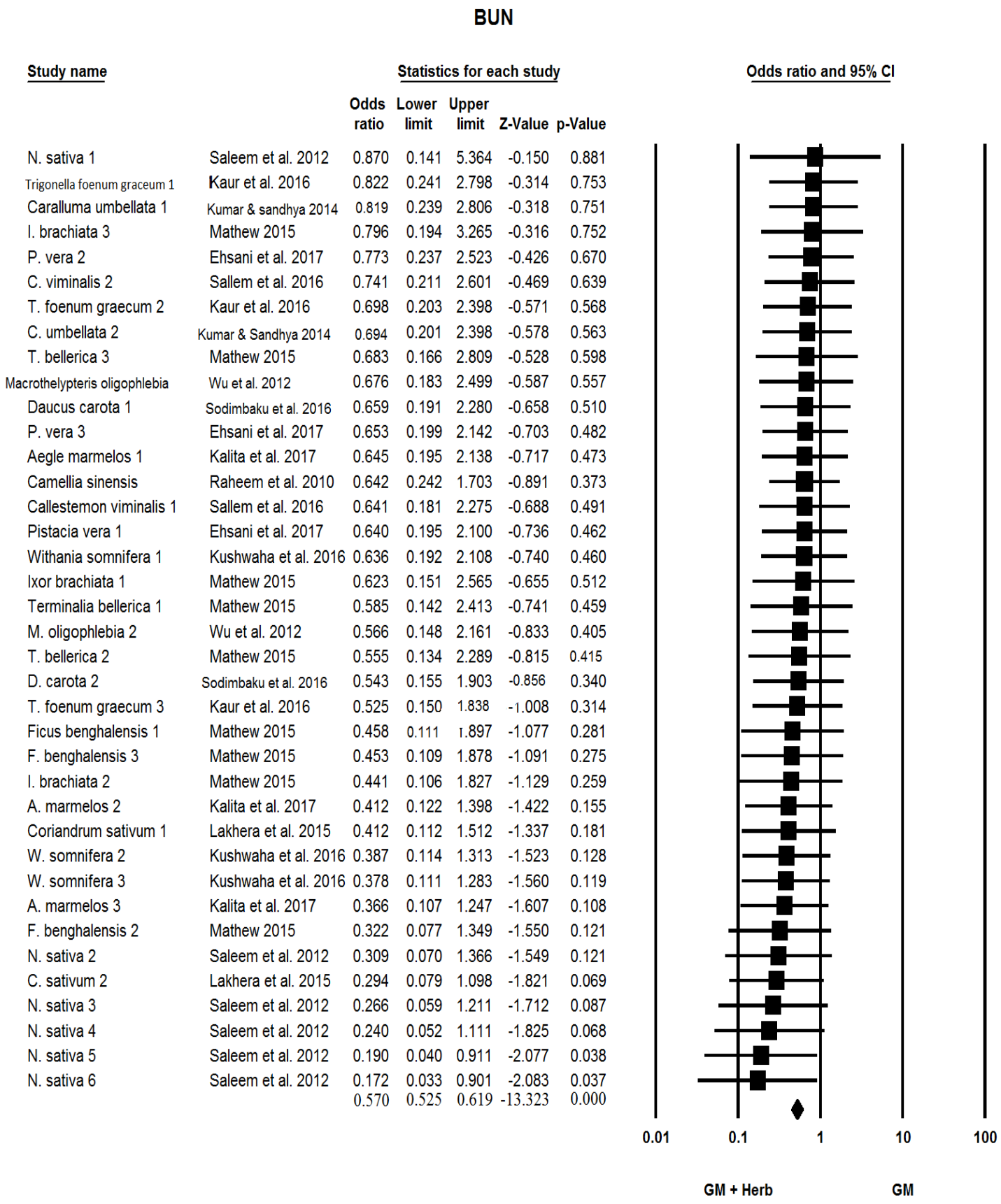

Fig. 3d. Forest plot analysis of BUN for nephroprotective species against gentamicin induced toxicity

URIC ACID

Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Tecoma stans	Mohan et al. 2016	2.033	0.343	12.067	0.781	0.435
Mentha piperita 1	Ullah et al. 2013c	1.171	0.073	18.769	0.112	0.911
Bacopa monneiri 1	Kannan et al. 2011	1.111	0.002	715.450	0.032	0.975
B.monneiri 2	Kannan et al. 2011	1.111	0.002	715.450	0.032	0.975
C. sativus 3	Omidi & Torabi 2016	1.084	0.399	2.946	0.157	0.875
C. sativus 2	Omidi & Torabi 2016	1.064	0.391	2.894	0.122	0.903
Petroselinum sativum	Shalaby & Hammouda 2014	1.020	0.085	12.311	0.016	0.987
Eruca sativa	Shalaby & Hammouda 2014	1.013	0.084	12.271	0.010	0.992
Citrullus colocynthis	Ullah et al. 2013b	1.013	0.120	8.535	0.012	0.991
Curcuma longa	Shalaby & Hammouda 2014	1.007	0.083	12.232	0.005	0.996
CL+ES+PS	Shalaby & Hammouda 2014	1.000	0.082	12.192	0.000	1.000
M. piperita 2	Ullah et al. 2013c	0.981	0.080	11.957	-0.015	0.988
C. sativus 1	Omidi & Torabi 2016	0.949	0.348	2.582	-0.103	0.918
Bauhinia variegata	Prusty et al. 2012	0.900	0.009	93.444	-0.044	0.965
Punica granatum	Primarizyk et al. 2016	0.897	0.069	11.623	-0.084	0.933
N. nucifera 3	Dubey et al. 2014	0.888	0.192	4.109	-0.153	0.879
Cinnamomum zeylanicum 1	Tanomand & Najafian 2013	0.850	0.185	3.906	-0.209	0.835
T. stans 1	Raju et al. 2011	0.841	0.152	4.655	-0.198	0.843
N. nucifera 2	Dubey et al. 2014	0.834	0.178	3.907	-0.230	0.818
Terminalia bellerica 1	Fatima and Sultana	0.809	0.155	4.226	-0.252	0.801
Beta vulgaris 1	El Gamal et al. 2014	0.782	0.142	4.309	-0.283	0.777
Gingko biloba 1	Mansoor et al. 2015	0.762	0.157	3.683	-0.339	0.735
T. stans 2	Raju et al. 2011	0.761	0.134	4.327	-0.308	0.758
Ferulago angulata 1	Valipour et al. 2016	0.749	0.119	4.714	-0.308	0.758
Jasminum grandiflorum 1	Venkataiah et al. 2013	0.732	0.147	3.640	-0.381	0.703
T. stans 3	Raju et al. 2011	0.716	0.124	4.144	-0.373	0.709
M. piperita 3	Ullah et al. 2013c	0.692	0.069	6.910	-0.313	0.754
T. bellerica 2	Fatima and Sultana	0.673	0.123	3.692	-0.353	0.649
Cinnamomum tamala	Ullah et al. 2013a	0.667	0.065	6.787	-0.342	0.732
Boerhavia diffusa 1	Padmini and Kumar 2013	0.648	0.027	6.484	-0.268	0.789
Cynara scolymus 1	Khattab et al. 2016	0.633	5.197	2.029	-0.770	0.441
N. nucifera 1	Dubey et al. 2014	0.626	0.125	3.125	-0.571	0.568
C. zeylanicum 2	Tanomand & Najafian 2013	0.625	0.127	3.066	-0.579	0.562
Tamarindus indica	Ullah et al. 2014b	0.603	0.056	6.486	-0.418	0.676
Trianthema portulacastrum	Vallabi and Elango 2015	0.601	0.080	4.542	-0.493	0.622
C. zeylanicum 3	Tanomand & Najafian 2013	0.588	0.118	2.926	-0.649	0.516
C. scolymus 2	Khattab et al. 2016	0.585	0.182	1.879	-0.901	0.368
Bauhinia purpurea 1	Laxmi et al. 2009	0.571	0.112	2.913	-0.673	0.501
F. angulata 2	Valipour et al. 2016	0.554	0.077	3.964	-0.588	0.556
G. biloba 2	Mansoor et al. 2015	0.546	0.104	2.871	-0.715	0.475
C. scolymus 3	Khattab et al. 2016	0.520	0.161	1.676	-1.095	0.274
B. vulgaris 2	El Gamal et al. 2014	0.517	0.082	3.253	-0.703	0.482
F. angulata 3	Valipour et al. 2016	0.492	0.065	3.735	-0.686	0.493
B. diffusa 2	Padmini and Kumar 2013	0.486	0.015	15.426	-0.409	0.682
Cuscuta reflexa 1	Alamgeer et al. 2017	0.484	0.030	7.914	-0.509	0.611
C. nucifera	Jose et al. 2017	0.462	0.086	2.483	-0.901	0.368
C. reflexa 2	Alamgeer et al. 2017	0.461	0.027	7.825	-0.536	0.592
B. purpurea 2	Laxmi et al. 2009	0.422	0.076	2.359	-0.982	0.326
C. reflexa 3	Alamgeer et al. 2017	0.394	0.020	7.619	-0.616	0.538
Portulaca oleracea	Mouhamed and Elshafeey 2011	0.367	0.073	1.837	-1.220	0.222

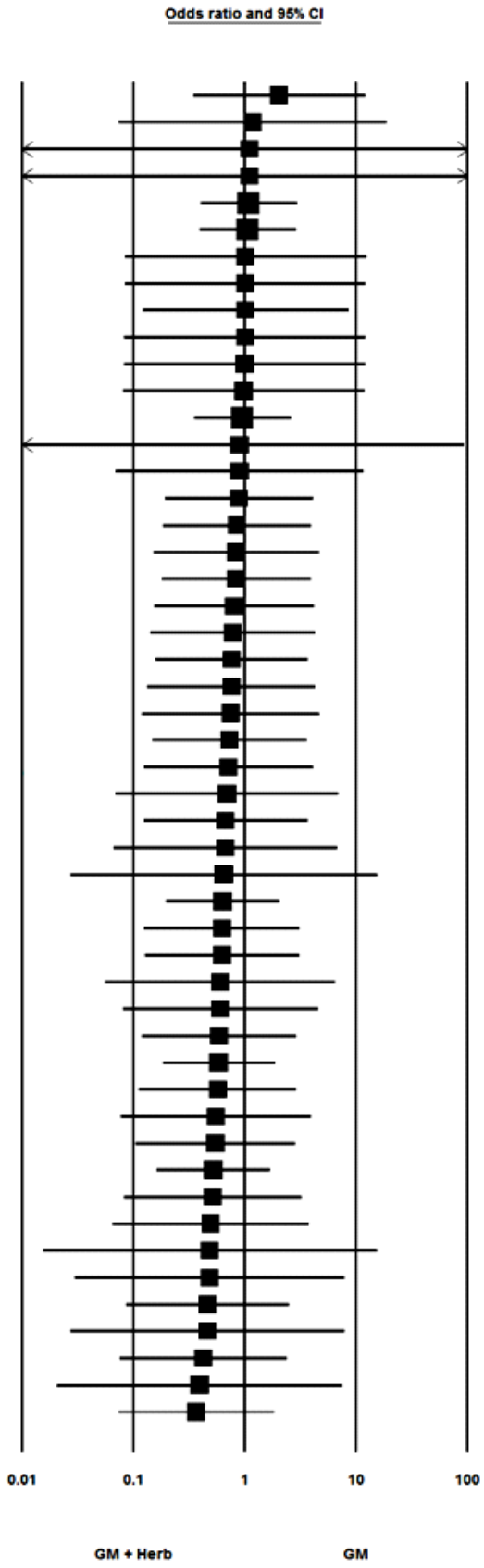

Fig. 4a. Forest plot analysis of Uric acid for nephroprotective species against gentamicin induced toxicity

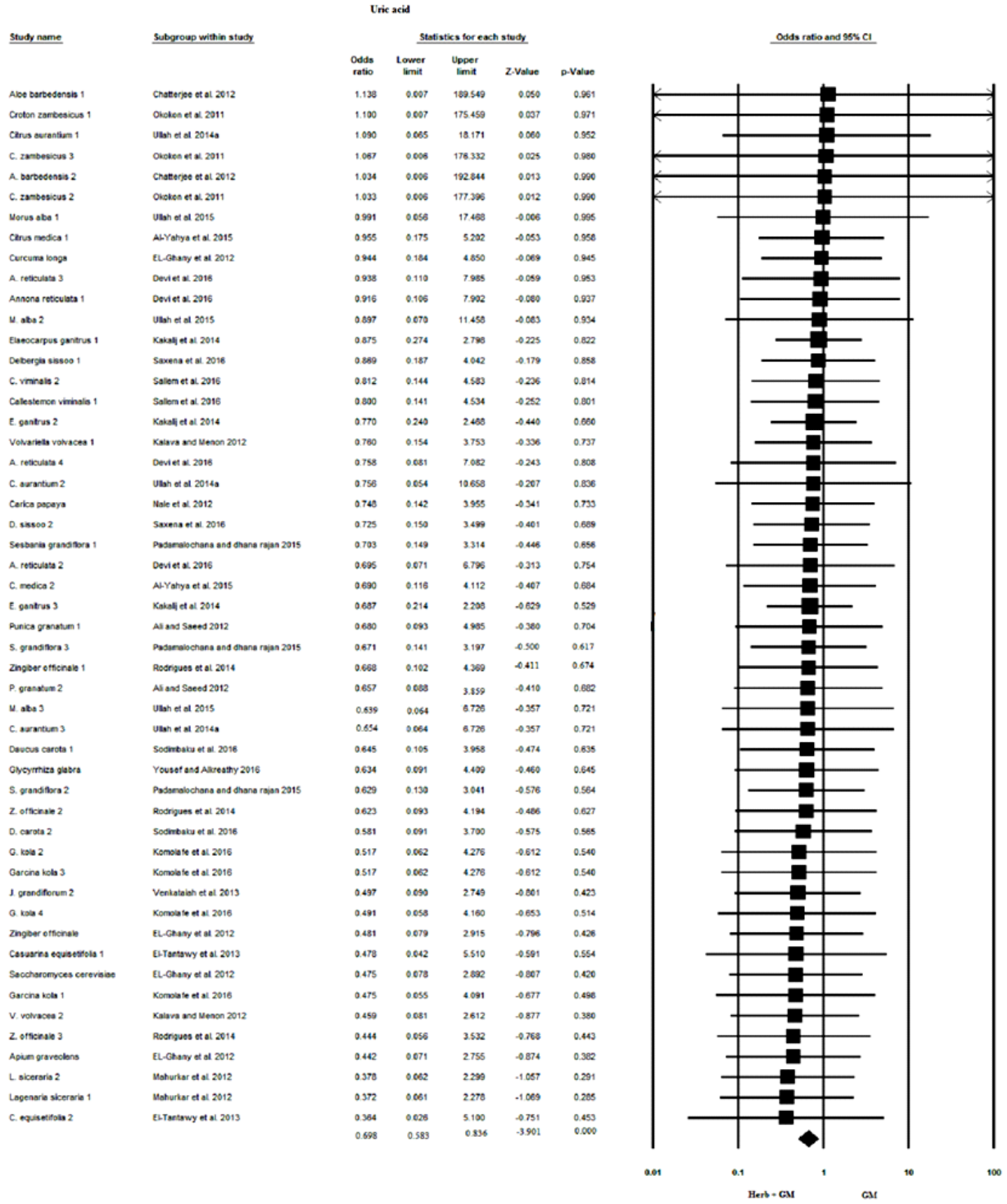

Fig. 4b. Forest plot analysis of Uric acid for nephroprotective species against gentamicin induced toxicity

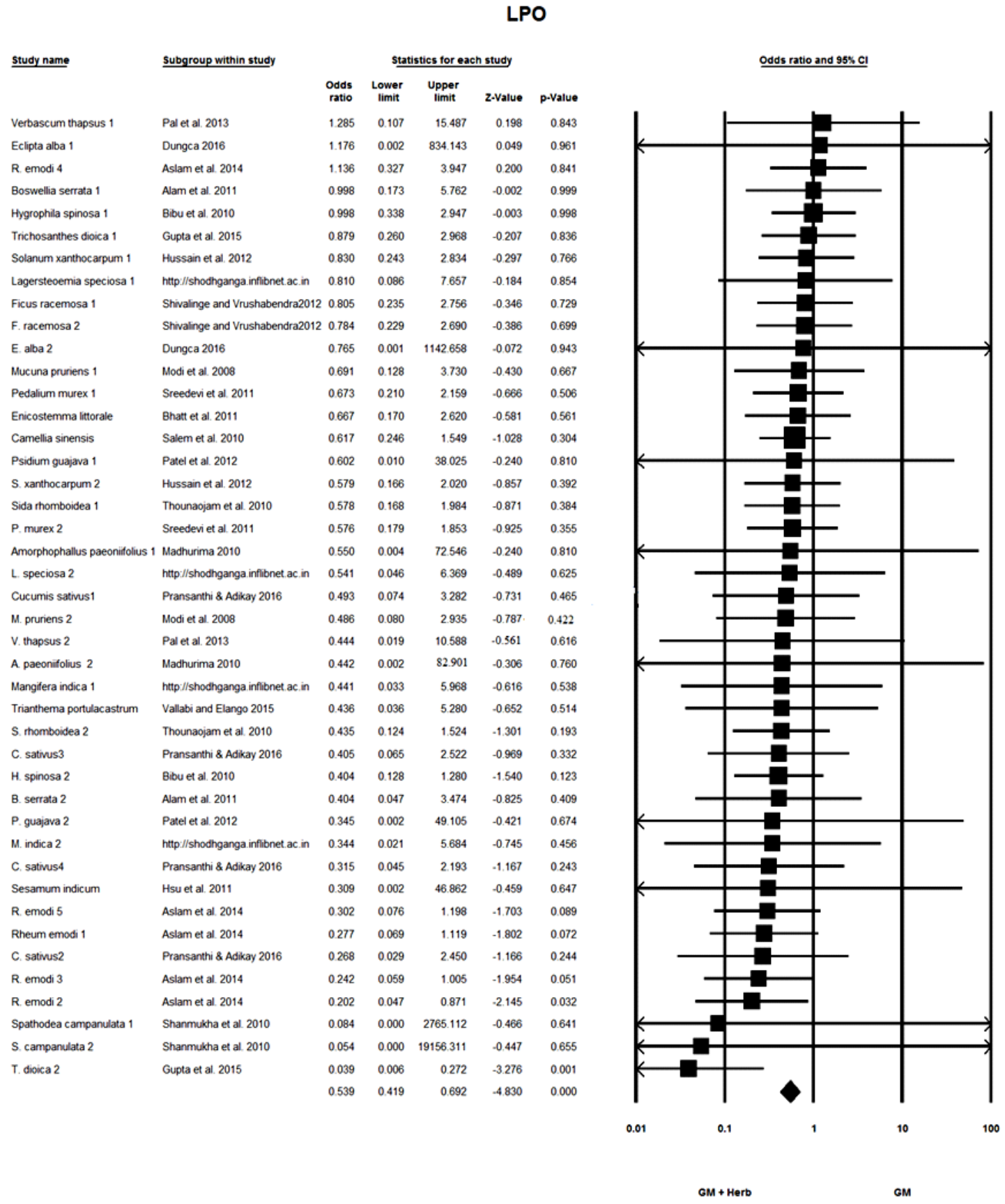

Fig. 5. Forest plot analysis of LPO for nephroprotective species against gentamicin induced toxicity

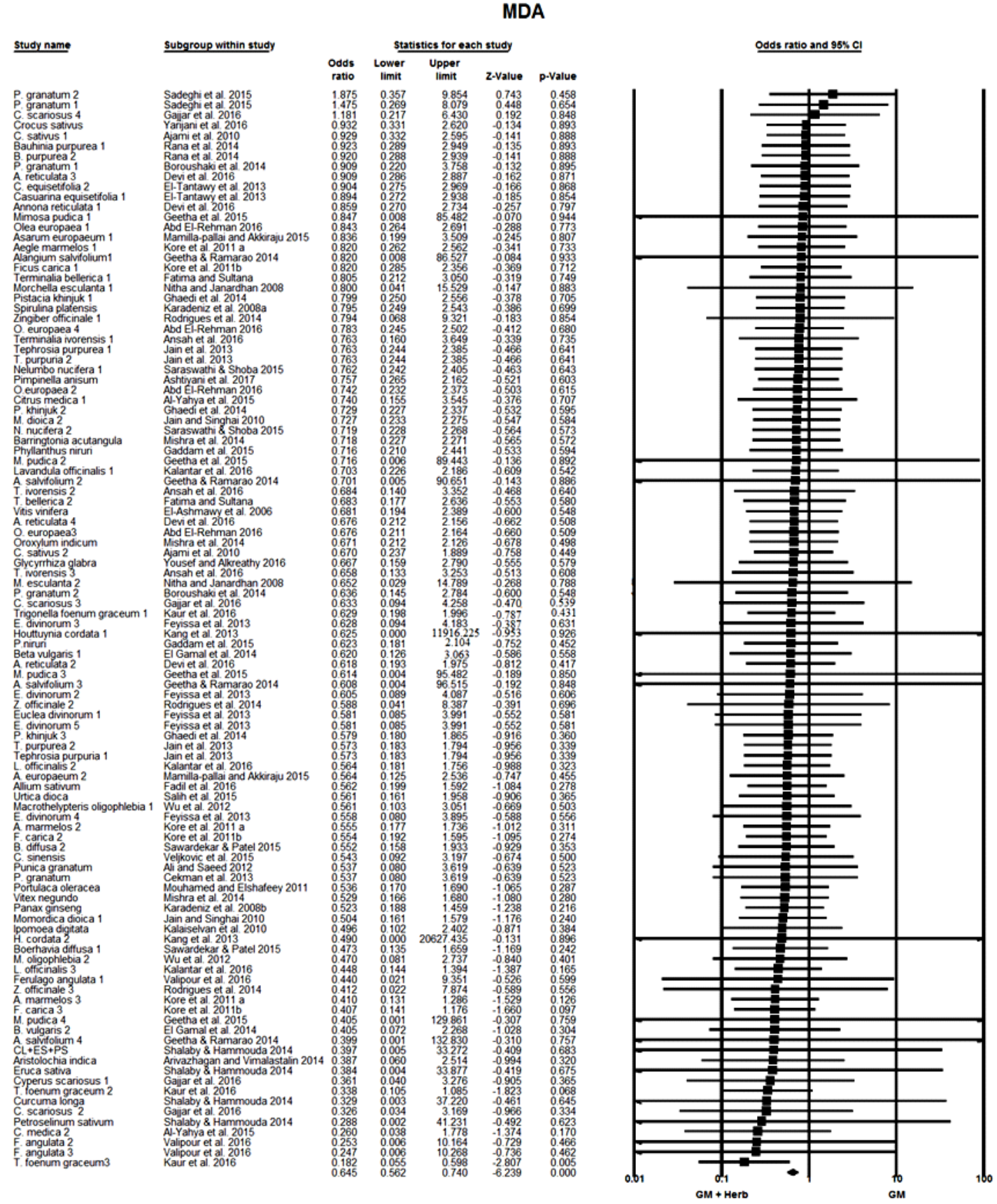

Fig. 6. Forest plot analysis of MDA for nephroprotective species against gentamicin induced toxicity

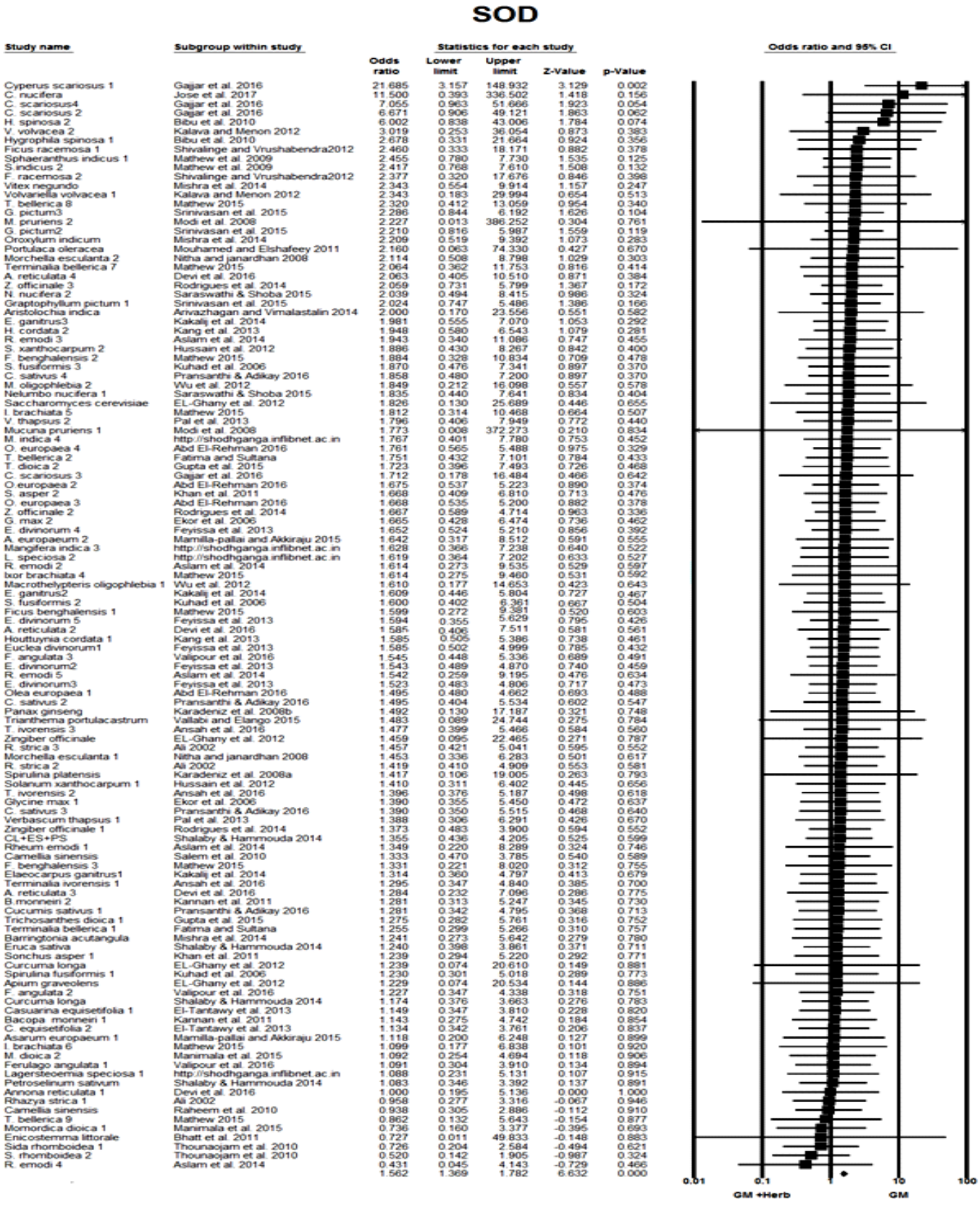

Fig. 7. Forest plot analysis of SOD for nephroprotective species against gentamicin induced toxicity

CAT

Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Portulaca oleracea	Mouhamed and Elshafeey 2011	9.000	0.000	2211717.583	0.495	0.621
E. divinorum 4	Feyissa et al. 2013	5.063	0.845	30.333	1.776	0.076
Euclea divinorum1	Feyissa et al. 2013	4.582	0.758	27.706	1.658	0.097
E. divinorum 5	Feyissa et al. 2013	4.268	0.701	25.994	1.574	0.115
A. marmelos 3	Kore et al. 2011 a	3.722	0.187	73.907	0.862	0.389
E. divinorum 2	Feyissa et al. 2013	3.703	0.598	22.913	1.408	0.159
E. divinorum 3	Feyissa et al. 2013	3.322	0.530	20.839	1.282	0.200
C. nucifera	Jose et al. 2017	2.950	0.450	19.321	1.128	0.259
G. pictum 3	Srinivasan et al. 2015	2.744	1.010	7.451	1.980	0.048
G. pictum 2	Srinivasan et al. 2015	2.669	0.982	7.248	1.925	0.054
V. thapsus 2	Pal et al. 2013	2.529	0.512	12.488	1.139	0.255
Graptophyllum pictum 1	Srinivasan et al. 2015	2.311	0.850	6.282	1.642	0.101
A. marmelos 2	Kore et al. 2011 a	2.295	0.098	53.696	0.517	0.605
Aristolochia indica	Arivazhagan and Vimalastalin 2014	2.262	0.451	11.342	0.992	0.321
S. asper 2	Khan et al. 2011	2.260	0.238	21.508	0.709	0.478
T. dioica 2	Gupta et al. 2015	2.071	0.567	7.563	1.102	0.271
S. xanthocarpum 2	Hussain et al. 2012	1.987	0.554	7.125	1.054	0.292
Verbascum thapsus 1	Pal et al. 2013	1.977	0.391	10.009	0.824	0.410
T. bellerica 2	Fatima and Sultana	1.903	0.443	8.180	0.865	0.387
A. salvifolium 3	Geetha & Ramarao 2014	1.816	0.663	4.976	1.160	0.246
Momordica dioica 1	Manimala et al. 2015	1.722	0.101	29.278	0.376	0.707
M. pudica 3	Geetha et al. 2015	1.611	0.589	4.405	0.928	0.353
Sonchus asper 1	Khan et al. 2011	1.610	0.153	16.963	0.396	0.692
Terminalia bellerica 1	Fatima and Sultana	1.556	0.354	6.835	0.585	0.559
F. angulata 3	Valipour et al. 2016	1.529	0.390	5.996	0.608	0.543
Barringtonia acutangula	Mishra et al. 2014	1.521	0.475	4.870	0.706	0.480
Trichosanthes dioica 1	Gupta et al. 2015	1.502	0.404	5.590	0.607	0.544
A. salvifolium 2	Geetha & Ramarao 2014	1.487	0.541	4.084	0.769	0.442
Vitex negundo	Mishra et al. 2014	1.484	0.463	4.753	0.664	0.507
A. salvifolium 4	Geetha & Ramarao 2014	1.472	0.536	4.043	0.750	0.458
S. nigrum	Priya and Venkatalakshmi 2011	1.461	0.286	7.455	0.456	0.649
N. nucifera 2	Saraswathi & Shoba 2015	1.446	0.377	5.548	0.567	0.591
F. angulata 2	Valipour et al. 2016	1.429	0.361	5.656	0.508	0.611
Aegle marmelos 1	Kore et al. 2011 a	1.411	0.947	42.458	0.198	0.843
Oroxylum indicum	Mishra et al. 2014	1.392	0.434	4.463	0.556	0.578
B.monneiri 2	Kannan et al. 2011	1.384	0.340	5.637	0.453	0.650
Rheum emodi 1	Aslam et al. 2014	1.369	0.431	4.342	0.533	0.594
Alangium salvifolium1	Geetha & Ramarao 2014	1.356	0.493	3.729	0.590	0.555
Solanum xanthocarpum 1	Hussain et al. 2012	1.326	0.362	4.862	0.425	0.671
R. emodi 3	Aslam et al. 2014	1.314	0.414	4.171	0.464	0.643
M. pudica 2	Geetha et al. 2015	1.307	0.477	3.583	0.520	0.603
M. pudica 4	Geetha et al. 2015	1.299	0.474	3.560	0.508	0.612
Ferulago angulata1	Valipour et al. 2016	1.286	0.320	5.169	0.354	0.723
Nelumbo nucifera 1	Saraswathi & Shoba 2015	1.285	0.332	4.983	0.363	0.716
R. emodi 2	Aslam et al. 2014	1.252	0.394	3.975	0.381	0.703
R. emodi 5	Aslam et al. 2014	1.239	0.390	3.936	0.364	0.716
Bacopa monneiri 1	Kannan et al. 2011	1.238	0.300	5.106	0.296	0.767
CL+ES+PS	Shalaby & Hammouda 2014	1.229	0.001	1394.599	0.057	0.954
Mimosa pudica 1	Geetha et al. 2015	1.222	0.445	3.352	0.389	0.697
B. vulgaris 2	El Gamal et al. 2014	1.183	0.273	5.117	0.225	0.822
Eruca sativa	Shalaby & Hammouda 2014	1.174	0.001	1431.909	0.044	0.965
Beta vulgaris 1	El Gamal et al. 2014	1.159	0.267	5.026	0.197	0.844
B. purpurea 2	Rana et al. 2014	1.133	0.350	3.661	0.208	0.835
Bauhinia purpurea 1	Rana et al. 2014	1.129	0.349	3.651	0.203	0.839
Curcuma longa	Shalaby & Hammouda 2014	0.938	0.001	1692.737	-0.017	0.987
M. dioica 2	Manimala et al. 2015	0.922	0.038	22.403	-0.050	0.960
Petroselinum sativum	Shalaby & Hammouda 2014	0.854	0.000	1851.756	-0.040	0.968
R. emodi 4	Aslam et al. 2014	0.818	0.256	2.612	-0.339	0.735

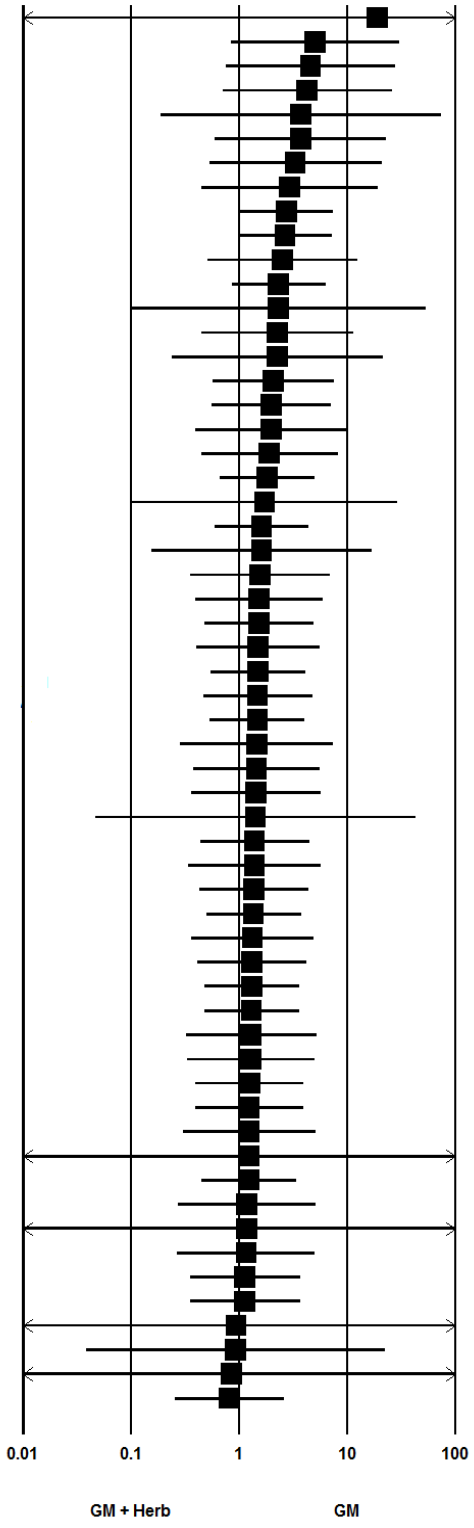

Fig. 8a. Forest plot analysis of CAT for nephroprotective species against gentamicin induced toxicity

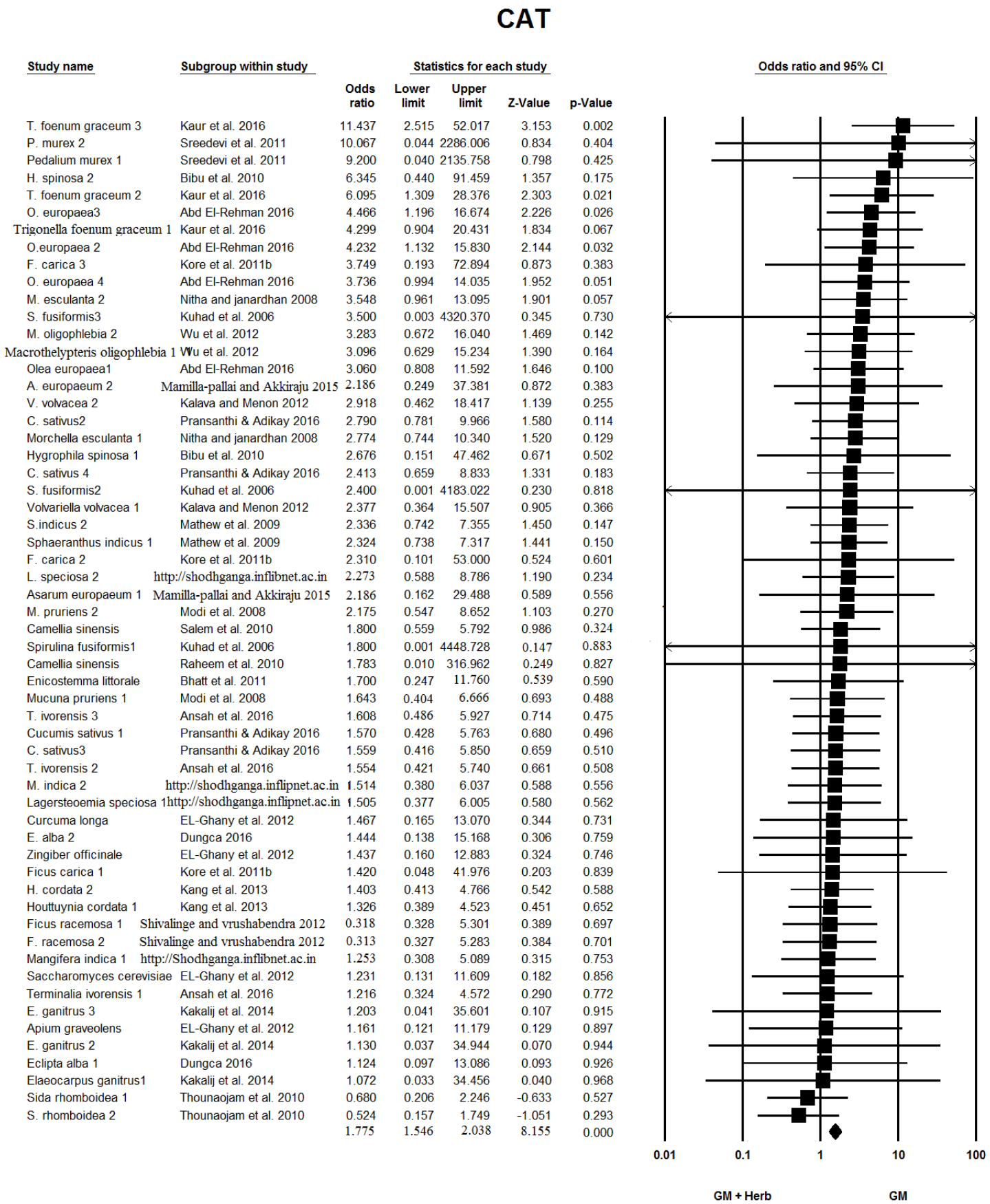

Fig. 8b. Forest plot analysis of CAT for nephroprotective species against gentamicin induced toxicity

GSH

Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
C. scariosus 2	Gajjar et al. 2016	7.321	2.218	24.163	3.268	0.001
C. scariosus 4	Gajjar et al. 2016	7.005	2.120	23.146	3.192	0.001
Portulaca oleracea	Mouhamed and Elshafeey 2011	5.556	0.000	3445307553382 23.000	0.106	0.916
S. fusiformis 3	Kuhad et al. 2006	3.811	0.989	14.684	1.944	0.052
V. thapsus 2	Pal et al. 2013	3.488	0.000	95317833144.660	0.102	0.919
A. marmelos 3	Kore et al. 2011 a	3.089	0.225	42.412	0.844	0.399
Boerhavia diffusa 1	Sawardekar & Patel 2015	2.667	0.767	9.277	1.542	0.123
B. diffusa 2	Sawardekar & Patel 2015	2.650	0.762	9.219	1.532	0.125
S. fusiformis 2	Kuhad et al. 2006	2.633	0.671	10.335	1.388	0.165
G. pictum 3	Srinivasan et al. 2015	2.628	0.649	10.646	1.354	0.176
Cyperus scariosus 1	Gajjar et al. 2016	2.493	0.722	8.601	1.445	0.148
A. marmelos 2	Kore et al. 2011 a	2.425	0.165	35.722	0.645	0.519
G. pictum2	Srinivasan et al. 2015	2.406	0.589	9.836	1.222	0.222
Graptophyllum pictum 1	Srinivasan et al. 2015	2.128	0.513	8.820	1.041	0.298
M. pudica 3	Geetha et al. 2015	2.111	0.000	612614.967	0.116	0.907
A. salvifolium 3	Geetha & Ramarao 2014	2.026	0.000	390396.997	0.114	0.909
O. gratissimum 2	Ogundipe et al. 2016	2.000	0.285	14.055	0.697	0.486
O. gratissimum 3	Ogundipe et al. 2016	2.000	0.285	14.055	0.697	0.486
M. pudica 2	Geetha et al. 2015	1.972	0.000	658781.411	0.105	0.917
Spirulina fusiformis 1	Kuhad et al. 2006	1.944	0.485	7.792	0.939	0.348
Ocimum gratissimum 1	Ogundipe et al. 2016	1.931	0.271	13.735	0.657	0.511
Tephrosia purpurea 1	Jain et al. 2013	1.928	0.553	6.722	1.030	0.303
T. dioica 2	Gupta et al. 2015	1.904	0.579	6.262	1.060	0.289
A. salvifolium 2	Geetha & Ramarao 2014	1.897	0.000	418232.265	0.102	0.919
N. sativa 2	Begum et al. 2006	1.844	0.153	22.258	0.482	0.630
Mimosa pudica 1	Geetha et al. 2015	1.833	0.000	718733.457	0.092	0.927
Alangium salvifolium 1	Geetha & Ramarao 2014	1.821	0.000	438549.126	0.095	0.925
M. dioica 2	Jain and Singhai 2010	1.813	0.519	6.337	0.932	0.351
S. xanthocarpum 2	Hussain et al. 2012	1.811	0.554	5.917	0.983	0.325
M. pudica 4	Geetha et al. 2015	1.778	0.000	747803.077	0.087	0.931
A. paeoniifolius 2	Madhurima 2010	1.775	0.035	91.131	0.286	0.775
R. emodi 5	Aslam et al. 2014	1.763	0.004	766.536	0.183	0.855
Rheum emodi 1	Aslam et al. 2014	1.740	0.004	767.229	0.178	0.859
P. granatum	Cekman et al. 2013	1.714	0.171	17.154	0.459	0.646
A. salvifolium 4	Geetha & Ramarao 2014	1.667	0.000	490330.050	0.080	0.937
R. strica 3	Ali 2002	1.655	0.149	18.346	0.411	0.681
R. emodi 2	Aslam et al. 2014	1.627	0.003	772.522	0.155	0.877
R. emodi 3	Aslam et al. 2014	1.627	0.003	772.522	0.155	0.877
P. guajava 2	Patel et al. 2012	1.615	0.090	28.950	0.346	0.745
N. sativa 3	Begum et al. 2006	1.606	0.126	30.220	0.364	0.716
C. scariosus 3	Gajjar et al. 2016	1.553	0.433	5.576	0.675	0.499
Nigella sativa 1	Begum et al. 2006	1.541	0.449	20.037	0.331	0.741
T. purpurea 2	Jain et al. 2013	1.493	0.425	5.262	0.623	0.533
Amorphophallus paeoniifolius 1	Madhurima 2010	1.476	0.025	86.285	0.188	0.851
Panax ginseng	Karadeniz et al. 2008b	1.444	0.406	5.132	0.567	0.570
Vitis vinifera	El-Ashmawy et al. 2006	1.429	0.282	7.240	0.431	0.667
T. bellerica 2	Fatima and Sultana	1.402	0.337	5.843	0.464	0.642
Spirulina platensis	Karadeniz et al. 2008a	1.381	0.340	5.608	0.452	0.651
N. nucifera 2	Saraswathi & Shoba 2015	1.381	0.080	23.819	0.222	0.824
R. strica 2	Ali 2002	1.379	0.117	16.326	0.255	0.799
Solanum xanthocarpum 1	Hussain et al. 2012	1.375	0.418	4.519	0.525	0.600
Nelumbo nucifera 1	Saraswathi & Shoba 2015	1.361	0.078	23.643	0.212	0.832
S. asper 2	Khan et al. 2011	1.357	0.036	51.308	0.165	0.869
CL + ES + PS	Shalaby & Hammouda 2014	1.348	0.417	4.357	0.499	0.618
Trichosanthes dioica 1	Gupta et al. 2015	1.329	0.401	4.408	0.465	0.642
Psidium guajava 1	Patel et al. 2012	1.322	0.067	26.220	0.183	0.855
Solanum nigrum	Priya and Venkatalakshmi 2011	1.319	0.216	8.068	0.300	0.764
M. dioica 1	Jain and Singhai 2010	1.301	0.367	4.621	0.408	0.684
Eruca sativa	Shalaby & Hammouda 2014	1.274	0.393	4.129	0.403	0.687
Terminalia bellerica 1	Fatima and Sultana	1.252	0.296	5.285	0.306	0.760
Aegle marmelos 1	Kore et al. 2011 a	1.249	0.064	24.562	0.146	0.884
Sonchus asper 1	Khan et al. 2011	1.196	0.029	49.605	0.094	0.925
B. monneiri 2	Kannan et al. 2011	1.175	0.283	4.873	0.222	0.824
Bacopa monneiri 1	Kannan et al. 2011	1.133	0.272	4.721	0.171	0.864
B. purpurea 2	Rana et al. 2014	1.083	0.262	4.466	0.110	0.913
Bauhinia purpurea 1	Rana et al. 2014	1.080	0.262	4.455	0.106	0.916
Curcuma longa	Shalaby & Hammouda 2014	1.060	0.323	3.473	0.096	0.923
Aristolochia indica	Arivazhagan and Vimalastalin 2014	1.050	0.111	9.891	0.043	0.966
Verbascum thapsus 1	Pal et al. 2013	1.042	0.000	7797650458755.500	0.003	0.998
Trianthema portulacastrum	Vallabi and Elango 2015	1.011	0.140	7.285	0.010	0.992
Momordica dioica 1	Manimala et al. 2015	0.964	0.144	6.469	-0.038	0.970
M. dioica 2	Manimala et al. 2015	0.940	0.139	6.359	-0.063	0.950
Petroselinum sativum	Shalaby & Hammouda 2014	0.932	0.282	3.080	-0.116	0.908
Rhazya strica 1	Ali 2002	0.841	0.056	12.623	-0.125	0.901
R. emodi 4	Aslam et al. 2014	0.645	0.000	1420.970	-0.112	0.911
Cocos nucifera	Jose et al. 2017	0.468	0.133	1.656	-1.177	0.239

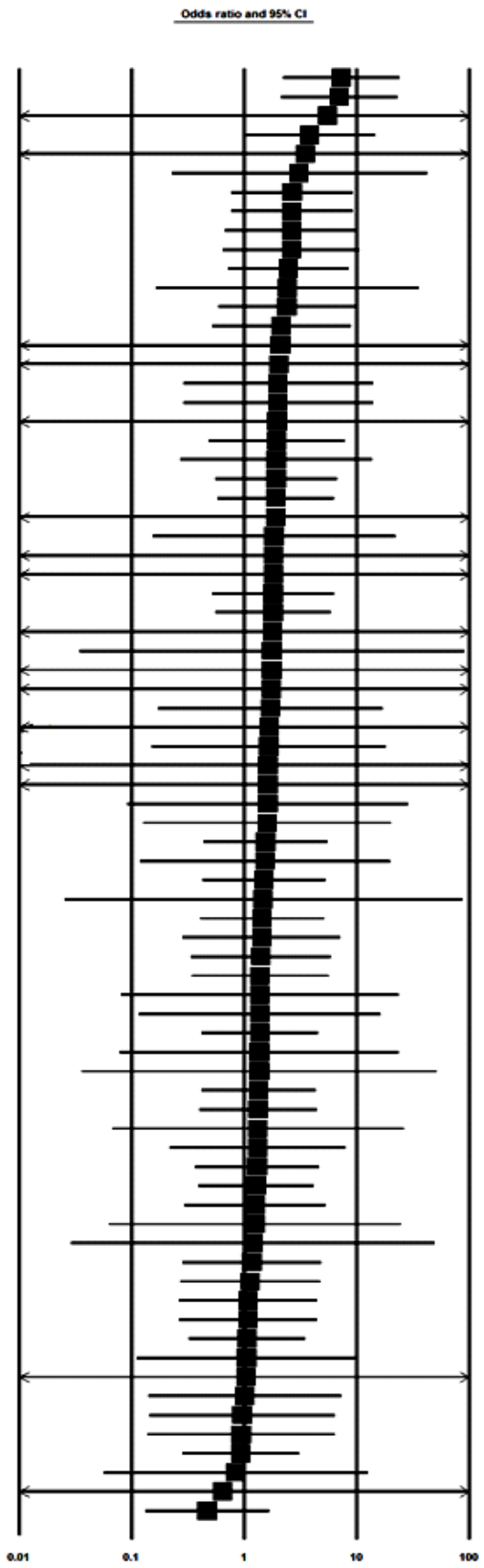

Fig. 9a. Forest plot analysis of GSH for nephroprotective species against gentamicin induced toxicity

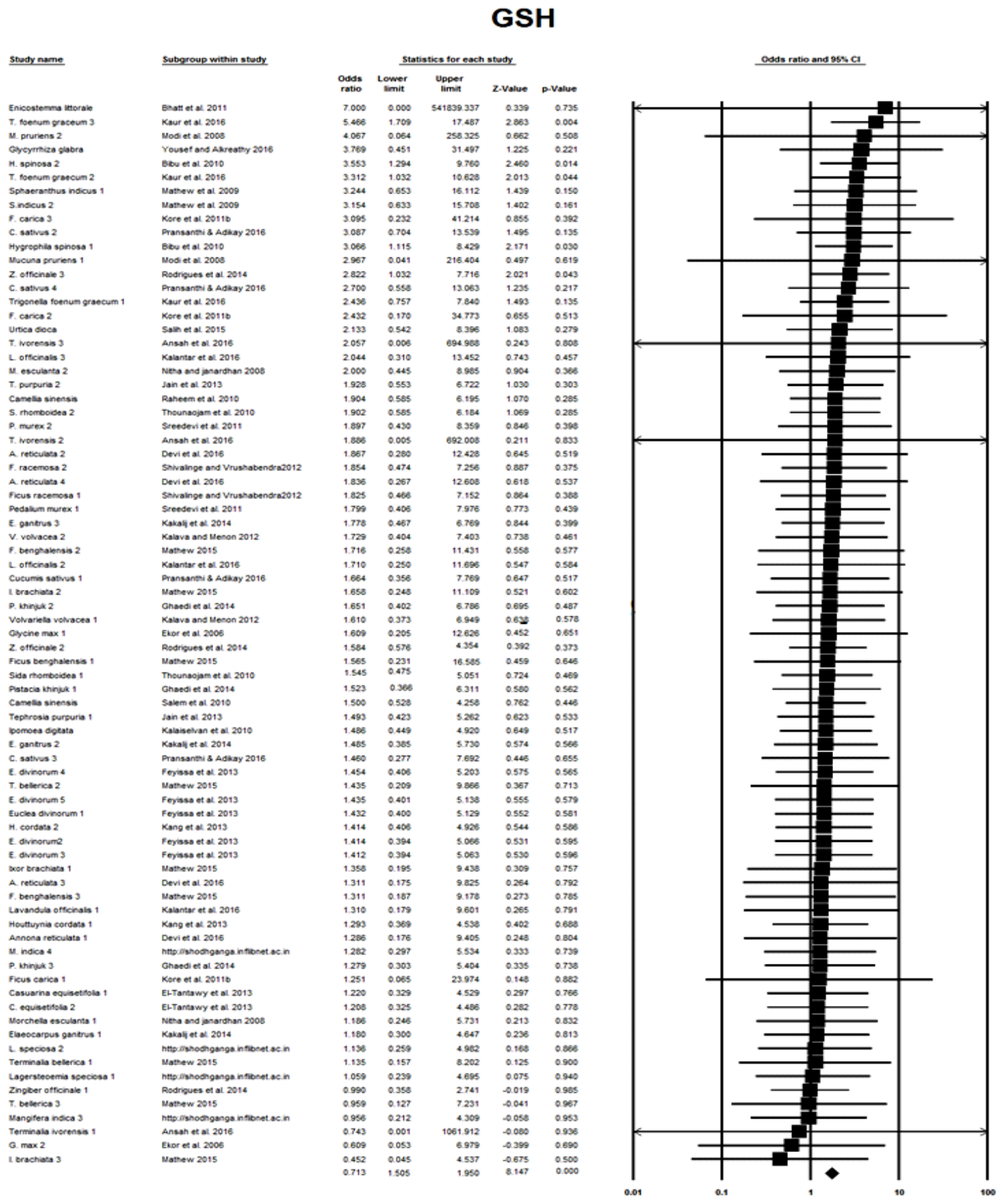

Fig. 9b. Forest plot analysis of GSH for nephroprotective species against gentamicin induced toxicity

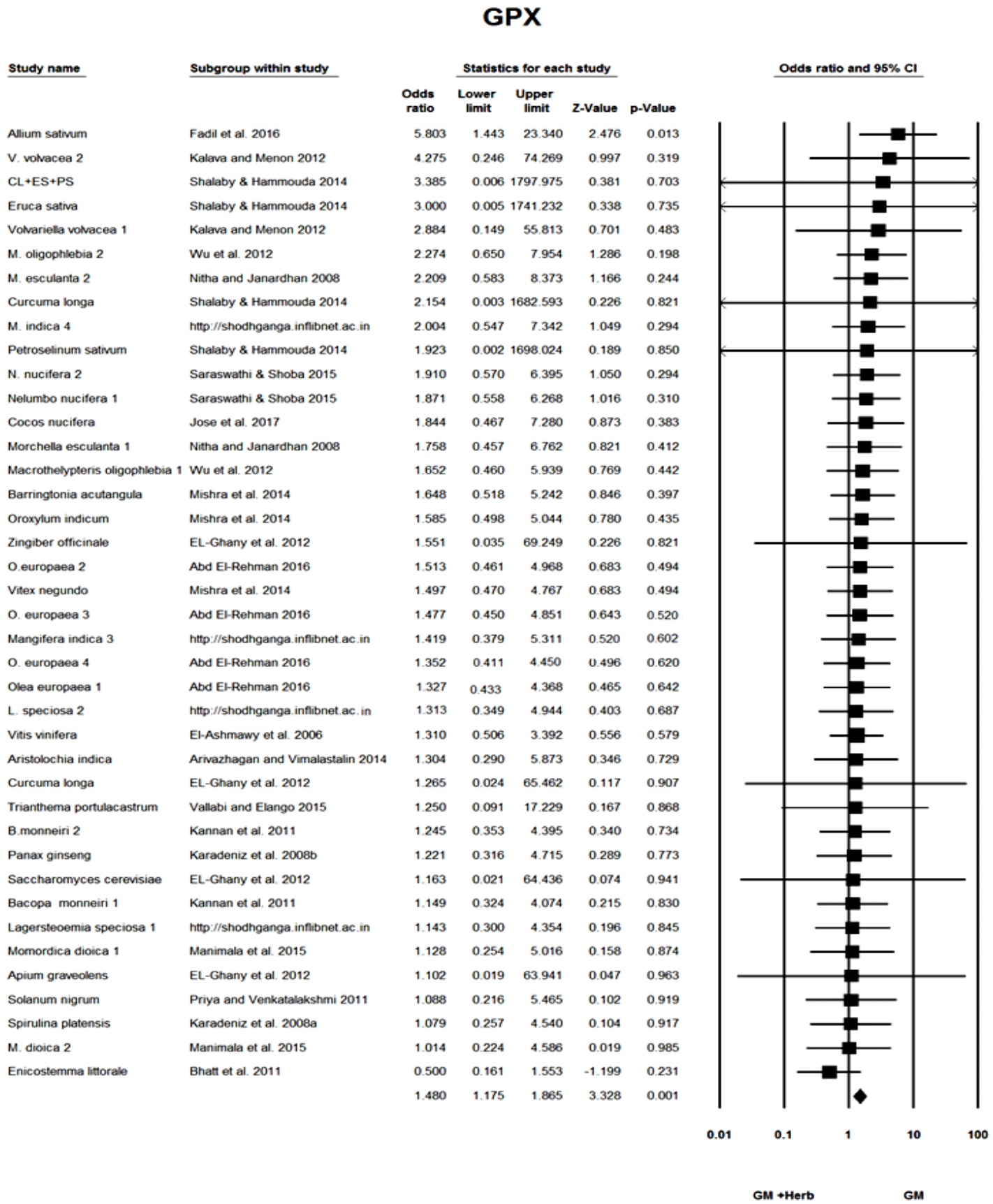

Fig. 10. Forest plot analysis of GPX for nephroprotective species against gentamicin induced toxicity

were on the left hand side of null effect line in the forest plots suggesting ameliorating role of herbal formulations in gentamicin treated animals (Fig. 1g, 2e, 3d, 4b, 5, 6). Considering point estimates for various parameters, overall effectiveness of herbal formulations were in the following order.

LPO> BUN>Creatinine>MDA=Urea>Uric acid

In contrast, values of Z, point estimate or odd ratio (RR) and CI were more than 1 for the overall study of antioxidants (Table 1) and diamonds were on the right hand side of null effect line in the forest plots suggesting reduction in the oxidative stress in the kidney of gentamicin treated animals (Fig. 7, 8b, 9b, 10). Based on point estimate values, overall effectiveness of plant extracts in maintaining higher antioxidant levels in the kidney of treatments was in the following order.

CAT>GSH>SOD>GPX

The odd ratios and CI values helped in classifying both least and most protective plant species (Table 2) whereas forest plots helped in indentifying relatively more ameliorative herbal treatments in which CI values did not overlap No Effect Line of forest plots (Fig. 1-10). Interestingly few most reno-protective species of Table 2 were missing in Table 3 because their CI values overlapped No Effect Line in the forest plots.

Maximum number of ameliorative species were recorded for serum urea (16 species) followed by blood urea nitrogen (8 species) while number declined for other parameters ranging between 3-4 species for creatinine, LPO, GSH, CAT and only single species for MDA, SOD and GP_X. Interestingly few species were found effective for 2-3 parameters; *Glycine max* and *Camelia sinensis* for urea and creatinine, *Nigella sativa* for urea and BUN, *Trigonella foenum graceum* for LPO, MDA, GSH, CAT and *Cyperus scariosus* for urea, SOD and GSH (Table 3).

Table 2. List of least and most protective plant species, and species having maximum percentage weightage in the overall studies for various parameters including their formulations

Parameters	Total no. of studies	Least Protective Plant Species			Most Protective Plant Species			Species having maximum % weightage	
		Species	Formulation	Odd ratio	Species	Formulation	Odd ratio	Species	Formulation
Creatinine	552	*Momordica dioica*	EtOH leaf extract (@ 200 mg/kg bw)	1.714	*Punica granatum*	Seed oil (@ 0.4 mL/kg bw)	0.057	*Camellia sinensis*	Tablet extract (@ 300 mg/kg bw)
Urea	404	*Tribulus terrestris* + *Crataeva nurvala*	Aq fruit extract (@ 65 mg/kg bw) + Aq bark extract (@ 65 mg/kg bw)	2.545	*Aristolochia indica*	MeOH leaf extract (@ 500 mg/kg bw)	0.104	*Piper cubeba*	Fruit Powder (@ 810 mg/kg bw)
BUN	220	*Althea officinalis*	EtOH fruit extract (@ 500 mg/kg bw)	2.222	*Myrmecodia tuberosa*	Aq. tuber extract (@ 4000 mg/kg bw)	0.052	*Panax ginseng*	Root Aq extract (@100 mg/kg bw)
Uric acid	101	*Tacoma stans*	Ethyl acetate flower extract (@ 100 mg/kg bw)	2.033	*Casuarina equisetifolia*	MeOH leaf extract (@ 300mg/kg bw)	0.364	*Crocus sativus*	EtOH petal extract (@ 80mg/kg bw)
LPO	43	*Verbascum thapsus*	MeOH leaf extract (@ 250 mg/kg bw)	1.285	*Trichosanthes dioica*	MeOH leaf extract (@400 mg/kg bw)	0.039	*Camellia sinensis*	Tablet extract (@300mg/kg bw)
MDA	106	*Punica granatum*	Seed oil (@0.4mL/kg bw)	1.875	*Trigonella foenum graceum*	Aq. seed extract (@ 800mg/kg bw)	0.182	*Ficus carica*	HydroEthanolic fruit extract (@ 750 mg/kg bw)
SOD	128	*Rheum emodi*	Chloroform rhizome extract (@ 50 mg/kg bw)	0.431	*Cyperus scariosus*	Hydroalcoholic root extract (@ 150 mg/kg bw)	21.685	*Camellia sinensis*	Tablet extract (@ 300 mg/kg bw)
Catalase	116	*Sida rhomboi-boidea*	Aq. leaf extract 400 mg/kg bw)	0.524	*Portulaca oleracea*	Aq. whole plant extract (@ 400 mg/kg bw)	19.0	*Cocos nucifera*	Cocos milk (@ 1mL/kg bw)
GSH	156	*Ixora brachiata*	Ethyl acetate leaf extract (@ 200 mg/kg bw)	0.452	*Cyperus scariosus*	Hydroalcoholic root extract (@ 150 mg/kg bw)	7.321	*Petroselinum sativum*	Powder whole plant (@ 5%)
GPX	40	*Enicost-emma littorale*	EtOH whole plant extract (@ 2500 mg/kg bw)	0.500	*Allium sativum*	Seed extract (@ 150 mg/kg bw)	5.803	*Vitis vinifera*	Aq seed extract (@ 150 mg/kg bw)

Abbreviation: Aq = Aqueous, EtOH = Ethanol, MeOH = Methanol

Table 3. List of significant studies recorded in meta-analysis of urea, creatinine, uric acid, BUN, LPO and MDA

S. No.	Plant species		Odd ratio
Urea			
1	*Aristolochia indica*	Lf MeOH Ext 500	0.104
2	*Costus afer*	Lf Aq Ext 375	0.117
3	*Spharanthes indicus*	WP EtOH Ext 300	0.183
4	*Nigella sativa*	Cur Seed oil 2mL/kg (26d)	0.186
5	*Casuarina equisetifolia*	Pre Lf MeOH Ext 300	0.201
6	*Spharanthes indicus*	WP EtOH Ext 150	0.241
7	*Glycine max*	Sd PeOH Ext 500	0.260
8	*Glycine max*	Sd PeOH Ext1000	0.260
9	*Piper cubeba*	Pre Fr Pow 810	0.260
10	*Punica granatum*	Con Fr Aq Ext 100	0.268
11	*Coriandrum sativum*	WP EtOH Ext 400	0.270
12	*Casuarina equisetifolia*	Cur Lf MeOH Ext 300	0.277
13	*Piper cubeba*	Pre Fr Pow1220	0.278
14	*Tribulus terrestris* + *Crataeva nurvala*	Pre Aq Fr extract 30 + Aq bark extract 30	0.289
15	*Boerhavia diffussa*	Con + Cur Rt 4000	0.298
16	*Piper cubeba*	Cur Fr Pow 810	0.302
17	*Cyperus scariosus*	Cur Rt HydAlc Ext 150	0.307
18	*Cyperus scariosus*	Cur Rt HydAlc Ext 150	0.310
19	*Benincasa hispida*	Sd EtOH Ext 500	0.322
20	*Camellia sinenesis*	Lf EtOH Ext 300	0.327
21	*Piper cubeba*	C Fr Pow 810	0.370
Creatinine			
1	*Glycine max*	Sd PeOH Ext 500	0.189
2	*Glycine max*	Sd PeOH Ext 1000	0.189
3	*Eclipta alba*	Lf EtOH Ext 300	0.220
4	*Eclipta alba*	Lf EtOH Ext 600	0.254
5	*Camellia sinenesis*	Lf EtOH Ext 300	0.321
BUN			
1	*Myrmecodia tuberosa*	Tuber Aq Ext 1000	0.052
2	*Myrmecodia tuberosa*	Tuber Aq Ext 2000	0.054
3	*Myrmecodia tuberosa*	Tuber Aq Ext 4000	0.163
4	*Nigella sativa*	Cur Seed oil 2mL/kg (20d)	0.172
4	*Panax ginseng*	Rt Aq Ext200	0.179
5	*Nigella sativa*	Cur Seed oil 2mL/kg (16d)	0.190
6	*Panax ginseng*	Rt Aq Ext 100	0.193
7	*Bauhinia purpurea*	Lf EtOH Ext 300	0.202
8	*Citrus aurantium*	Fr EtOH Ext 200	0.245
9	*Mentha piperata*	Lf EtOH Ext 200	0.256
10	*Sida cordifolia*	Lf EtOH Ext 200	0.273
11	*Allium sativum*	Con Clove EtOH Ext 20	0.293
SOD			
1	*Cyperus scariosus*	Cur Rt HydAlc Ext 150	21.685
LPO			
1	Trichosanthes dioica	Lf MeOH Ext 400	0.039
2	Rheum emodi	Rh SB Ext 50	0.202
MDA			
1	Trig*onella foenum graceum*	Sd Aq Ext 800	0.182
GP_X			
1	*Allium sativum*	Clove Aq Homo 500	5.803
GSH			
1	*Cyperus scariosus*	Cur Rt HydAlc Ext 150	7.321
2	*Cyperus scariosus*	Cur Rt HydAlc Ext 250	7.005
3	*Trigonella foenum graceum*	Sd Aq Ext 800	5.466
4	*Hygrophilla spinosa*	WP EtOH Ext 250	3.553
5	*Hygrophilla spinosa*	WP EtOH Ext 50	3.066
6	*Zingiber officinale*	Rh gingerol fraction 25	2.822
7	*Trigonella foenum graceum*	Sd Aq Ext 400	3.312
CAT			
1	*Trigonella foenum graceum*	Sd Aq Ext 800	11.437
2	*Trigonella foenum graceum*	Sd Aq Ext 400	6.095
3	*Olea europaea*	Lf EtOH Ext 80	4.466
4	*Olea europaea*	Lf EtOH Ext 40	4.232
5	*Graptophyllum pictum*	Lf PeOH Ext 300	2.744

Abbreviation: Fr = Fruit, Lf = Leaf, Rh = Rhizome, Rt = Root, Sd =Seed, WP = Whole plant
Aq= Aqueous, Con = Concomitant, Cur = Curative, EtOH = Ethanol, Ext = Extract, Hex =Hexane, Homo = Homogenate, HydAlc = Hydroalcoholic, MeOH= Methanol, PeOH = Phenol, Pow = Powder, Pre = Preventive, SB = Sodium bicarbonate

Because I^2 values for all the parameters were negative suggesting all studies to be homogenous and findings were statistically highly significant ($p = 0.000$) affirming reno-protection at the met analysis level to gentamicin + plant extract treatments in comparison to control.

Perusal of funnel plots for urea, creatinine, BUN, uric acid, SOD, CAT, GSH, GPX, LPO and MDA revealed maximum numbers of studies converging at the tip of funnel were almost equally distributed on both sides of average line on account of lower SEM while fewer studies having higher SEM were distributed at the base (Fig. 11,12). The range of log odd ratios affected shape of funnel. Its narrower range reduced base for funnel plots of urea, uric acid, BUN, creatinine in comparison to SOD, catalase, GSH, GPX, LPO and MDA. All dots were within funnel plots for uric acid, creatinine, MDA, GPX and GSH whereas few dots (1-4) were outside funnel plots for urea, BUN, SOD, CAT and LPO. These findings suggest unbiasness in the publications. Further majority of the studies were more precise since these were closer to the average value and having lesser standard error.

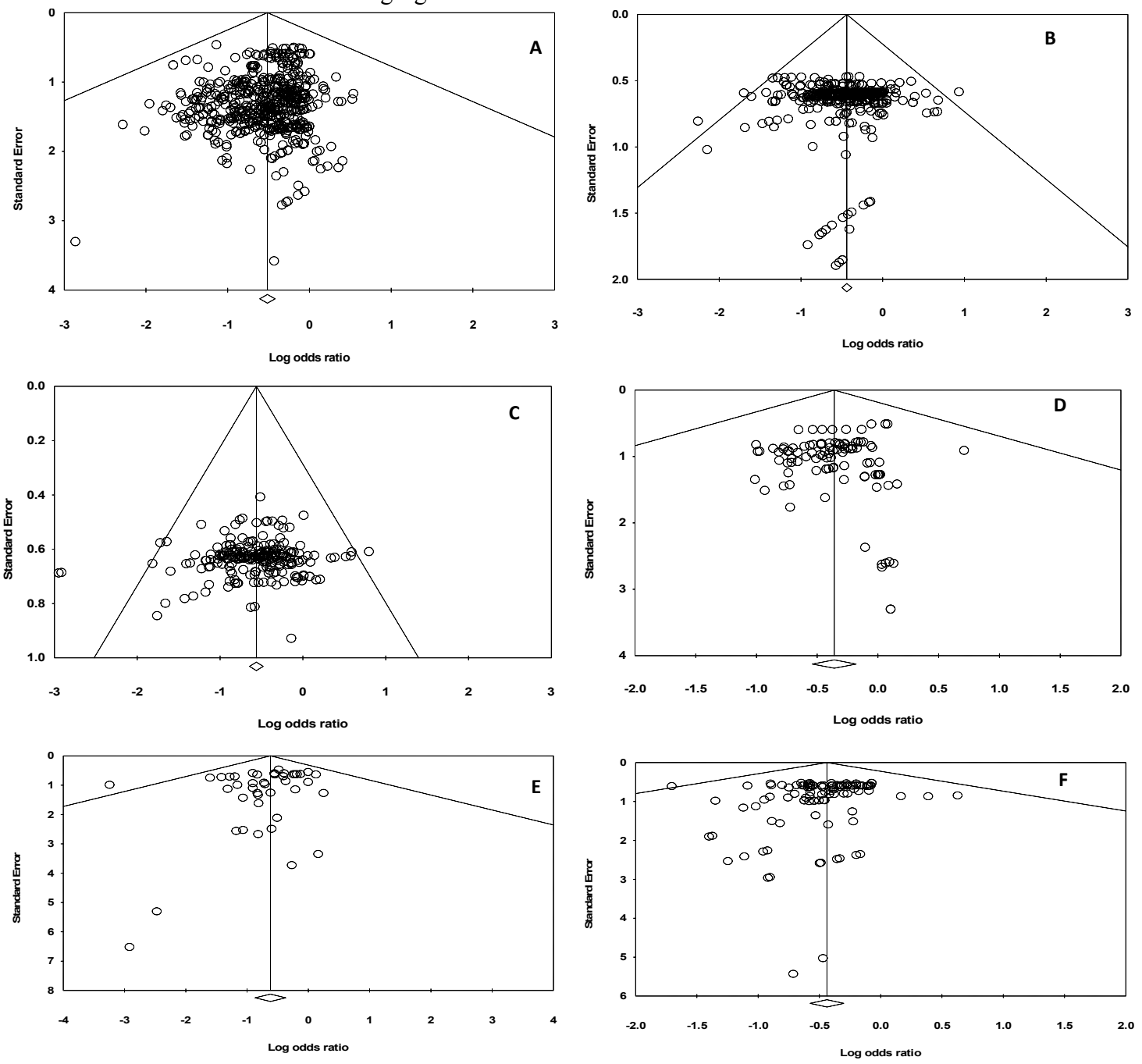

Fig. 11. Funnel plot analysis for Creatinine (A), Urea (B), Blood urea nitrogen (BUN) (C), Uric acid (UA) (D), LPO (E) and MDA (F) for nephro-protective species against gentamicin induced toxicity

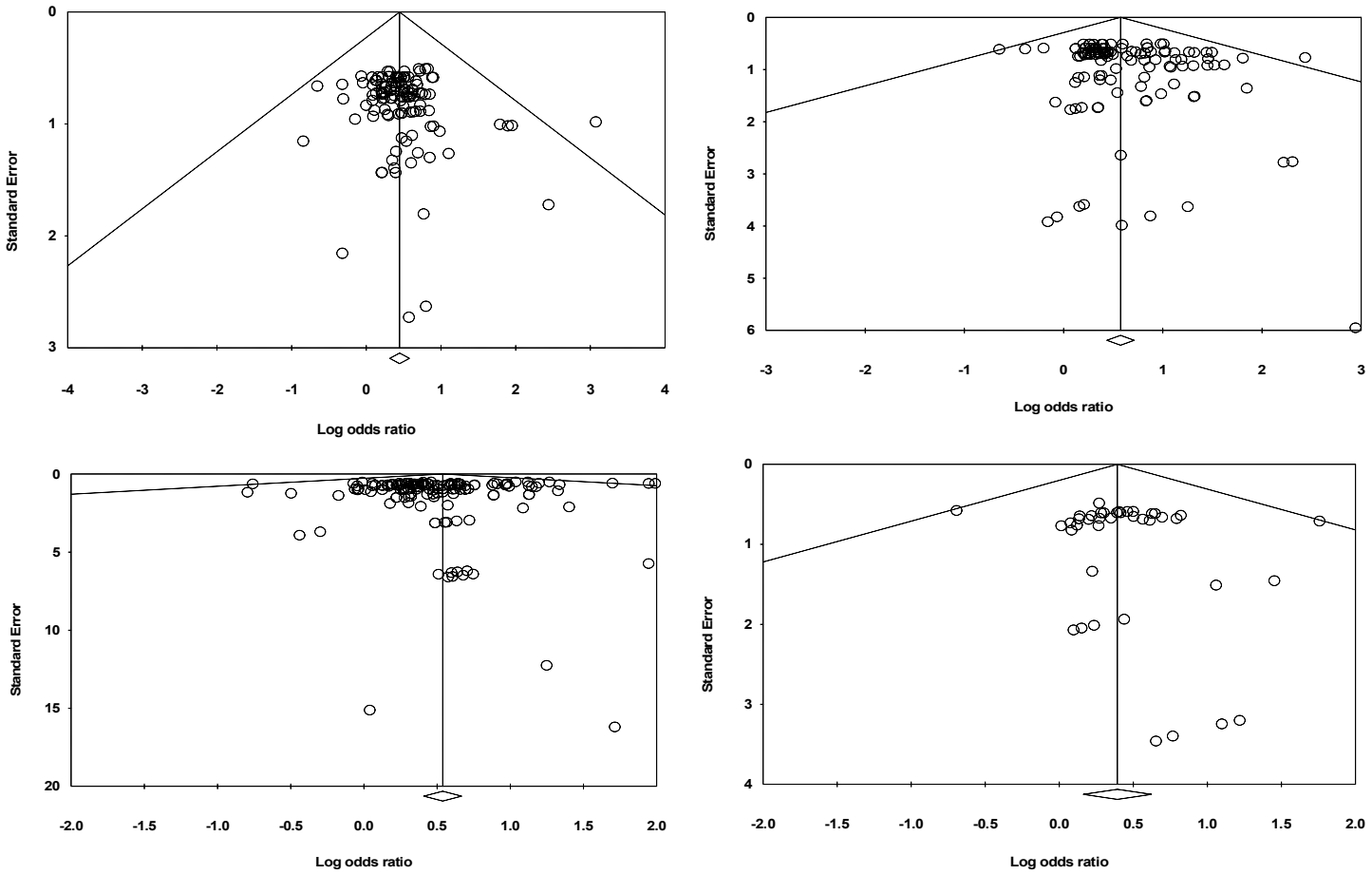

Fig. 12. Funnel plot analysis for SOD (A), Catalase (B), GSH (C), GPX(D) for nephroprotective species against gentamicin induced toxicity

CONCLUSION

During meta-analysis, plant species in combination were found more renoprotective in comparison to individual species (Fig. 1-10). We therefore, suggest that ameliorative role of the most protective plant species listed in Table 2 and 3 may be explored further in combination for formulating most potent renoprotective drug. Interestingly many of these species not only grows abundantly but also consumed since ages as fruit (*Punica granautm*), hot/cold drink (*Camellia sinensis*), in the preparation of cuisines (*Allium sativum*, *Citrus aurantium*, *Coriandrum sativum*, *Mentha piperata*, *Trigonella foenum graceum*, *Trichosanthes dioica*, *Zingiber officinale*, *Nigella sativa*) and drugs in India (Ayurvedic) and other Asian countries (*Boerhavia diffusa*, *Piper cubeba*, *Myrmecodia tuberose*, *Eclipta alba*, *Hygrophilla spinosa*, *Panax ginseng*, *Tribulus terrestris*, *Crataeva nurvula*, *Sida cordifolia*, *Rheum emodi*, *Bauhinia purpurea*, *Cyperus scariosus*, *Aristolochia indica*). These locally growing/available species may play an important role in the healthcare of rural areas where access to modern medicare is poor and also people have strong belief in the herbal medicines.

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